

The American Journal of Medicine

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CONTENTS OF VOLUME V

ORIGINAL ARTICLES

Retrospect and Prospect, 1948	<i>Alexander B. Gutman</i>	1
Antistreptolysin "O." A Study of This Antibody in Health and in Hemolytic Streptococcus Respiratory Disease in Man	{ <i>Lowell A. Rantz</i> <i>Elizabeth Randall</i> <i>Helen H. Rantz</i>}	3
Streptococcal Fibrinolysin (Streptokinase). A Study of This Substance and Its Antibody in Group A Hemolytic Streptococcus Sore Throat	{ <i>Lowell A. Rantz</i> <i>Paul J. Boisvert</i>}	24
Immediate Pressor Effect of Desoxycorticosterone Acetate in Arterial Hypertension	{ <i>Melvin L. Goldman</i> <i>Henry A. Schroeder</i>}	33
Prolongation of the Coagulation of Whole Blood by Dicumarol in Man	{ <i>William C. Moloney</i> <i>Albert S. Murphy</i> <i>William J. Harrington</i>}	40
Thephorin in Allergy. A Study of 292 Cases	{ <i>Ephraim B. Cohen</i> <i>Helen P. Davis</i> <i>William A. Mowry</i>}	44
Agranulocytosis during Propylthiouracil Therapy	<i>Elmer C. Bartels</i>	48
Acute Porphyria. Two Cases with Autopsy Reports	{ <i>Laura Hare</i> <i>Ralph Wilmore</i>}	53
Spontaneous Mediastinal Emphysema and Pneumothorax.	<i>Arthur J. Draper</i>	59
Pyoderma Gangrenosum in Chronic Non-specific Ulcerative Colitis. A Report of Three Cases	{ <i>William E. Ricketts</i> <i>Joseph B. Kirsner</i> <i>Stephan Rothman</i>}	69
Unusual Strain of <i>Pseudomonas Aeruginosa</i> Recovered from the Urinary Bladder. Effects of Streptomycin	{ <i>Joseph A. Lazarus</i> <i>Lewis H. Schwarz</i>}	76
What Value Enteric Coating	<i>Joseph B. Wolffe</i>	87
Status of Antithyroid Substances in Thyroid Disease	<i>Thomas Hodge McGavack</i>	90
Effect of Injury and Disease on Nitrogen Metabolism.	<i>John P. Peters</i>	100
Management of Disorders of Cardiac Rhythm		110
Progressive Congestive Heart Failure with Peripheral Vascular Collapse		126
Thiouracil Hepatitis	{ <i>J. E. Holoubek</i> <i>W. R. Mathews</i> <i>W. J. Hollis</i>}	138
Rupture of Splenic Infarct and Sudden Death Complicating the Course of Subacute Bacterial Endocarditis.	<i>Charles A. Rosenberg</i>	143
Complications of Deep X-ray Therapy of Carcinoma of the Lung	<i>Victor C. Jacobsen</i>	148
American Federation for Clinical Research—Abstracts of Papers Presented at the Eastern Sectional Meeting, December, 1947		157

Contents

iii

Problems of Convalescence	<i>George Draper</i>	165
Pulmonary Paragonimiasis	{ <i>Alvin J. B. Tillman</i> <i>Harry S. Phillips</i> }	167
Studies on Patients with Cirrhosis of the Liver. Plasma and Liver Lipid Distribution and Its Relation to the Pathology of the Liver	{ <i>George H. Stueck, Jr.</i> <i>Saul H. Rubin</i> <i>Delphine H. Clarke</i> <i>Irving Graef</i> <i>Elaine P. Ralli</i> }	188
Renal Tubular Excretory Capacity for Penicillin in Health and in Subacute Bacterial Endocarditis.	{ <i>Sergius Bryner</i> <i>William H. Clark</i> <i>Elizabeth Randall</i> <i>Lowell A. Rantz</i> }	202
Pulmonary Atelectasis in Stuporous States. A Study of Its Incidence and Mechanism in Sodium Amytal Narcosis	{ <i>Roy Laver Swank</i> <i>Magnus I. Smedal</i> }	210
Prognosis in Gastric Cancer. A Study of Five-year Survivors	{ <i>Samuel N. Maimon</i> <i>Walter Lincoln Palmer</i> <i>Joseph B. Kirsner</i> }	230
Benign Pelvic Tumors with Ascites and Hydrothorax. Meigs' Syndrome	{ <i>Wilfred E. Wooldridge</i> <i>Paul O. Hagemann</i> }	237
Metabolic and Inflammatory Histiocytosis. With Case Reports of Gaucher's Disease, Letterer-Siwe's Disease and Eosinophilic Granuloma	<i>Bernard Straus</i>	245
Cor Pulmonale. Observations on Forty-two Autopsied Patients	{ <i>Samuel D. Spatt</i> <i>David M. Grayzel</i> }	252
Urinary Calculi	<i>John Kingsley Lattimer</i>	256
Problems in the Evaluation of Protein Therapy	<i>F. Homburger</i>	264
A Case of Hysteria		272
Obesity, Hypertension, Diabetes and Heart Failure		277
Lupus Erythematosus Disseminatus Sine Lupo with the Nephrotic Syndrome	{ <i>Joel J. Brenner</i> <i>William A. Leff</i> <i>Elliott Hochstein</i> }	288
Hemolytic Staphylococcus Albus Bacteremia and Pericarditis Treated with Sodium Salt of Penicillin and Penicillin in Beeswax and Peanut Oil	<i>John H. Bland</i>	298
Congenital Dextrocardia Complicated by Hypertension, Coronary Artery Disease and Myocardial Infarction	{ <i>Addison L. Messer</i> <i>Charles K. Donegan</i> <i>Edward S. Orgain</i> }	304
Bromsulfalein Reaction	{ <i>William N. Chambers</i> <i>F. Corbin Moister</i> }	308
American Federation for Clinical Research—Abstracts of Papers Presented at the Southern Sectional Meeting, January, 1948		311
Coronary Arteries as End Arteries	<i>Herrman L. Blumgart</i>	321

A Study of Specialized Heart Tissue at Various Stages of Development of the Human Fetal Heart	{ <i>Jane Sands Robb</i> . . . <i>Cornelius T. Kaylor</i> . . . <i>William G. Turman</i> . . . }	324
Abnormal Electrocardiograms in the Absence of Demonstrable Heart Disease	<i>David Littmann</i> . . .	337
Asymptomatic Heart Disease. Observations Made during the Early Recruiting Period for Navy and Marine Enlistments	<i>Albert Salisbury Hyman</i> . . .	351
Significance of Electrocardiographic Changes in Rheumatic Fever	<i>Maurice Sokolow</i> . . .	365
Oxygen Therapy in Acute Rheumatic Carditis in Children	{ <i>Leo M. Taran</i> . . . <i>Nelly Szilagyi</i> . . . }	379
Effect of Oxygen Therapy on the Electrical Sequence of Events in the Cardiac Cycle in Children with Acute Rheumatic Carditis	{ <i>Leo M. Taran</i> . . . <i>Nelly Szilagyi</i> . . . }	392
The Treatment of Pneumococcal Meningitis	{ <i>Geo. W. Waring, Jr.</i> . . . <i>Louis Weinstein</i> . . . }	402
Utilization of Protein Hydrolysates by Normal and Protein-Depleted Animals	<i>James B. Allison</i> . . .	419
Peripheral Vascular Disease		433
Pneumococcal Meningitis		449
Simmonds' Disease	{ <i>Benjamin Rosenberg</i> . . . <i>Julius Rosenthal</i> . . . <i>Gustav J. Beck</i> . . . }	462
Friedländer Bacillus Meningitis Successfully Treated with Streptomycin. Consideration of Friedländer Bacillus Infections in Diabetes	<i>L. Fred Ayvazian</i> . . .	470
"Intractability" in Peptic Ulcer	<i>Walter Lincoln Palmer</i> . . .	479
Lysozyme Activity in Ulcerative Alimentary Disease.	{ <i>Karl Meyer</i> . . . <i>John F. Prudden</i> . . . <i>William L. Lehman</i> . . . <i>Anita Steinberg</i> . . . }	482
I. Lysozyme in Peptic Ulcer		
II. Lysozyme Activity in Chronic Ulcerative Colitis	{ <i>Karl Meyer</i> . . . <i>Alfred Gellhorn</i> . . . <i>John F. Prudden</i> . . . <i>William L. Lehman</i> . . . <i>Anita Steinberg</i> . . . }	496
Bleeding Peptic Ulcer. A Review of Fifty-seven Consecutive Cases	{ <i>Ralph Lee Fisher</i> . . . <i>Morris Zukerman</i> . . . <i>E. Henry Keutmann</i> . . . <i>Harold A. Friedman</i> . . . <i>Samuel H. Bassett</i> . . . <i>Charles D. Kochakian</i> . . . <i>Ella M. Russ</i> . . . }	503
Metabolic Studies in Cushing's Syndrome. Treatment with Various Androgens and a Six-year Follow-up		518
Insulin Mixtures and Conservation of Insulin	<i>Russell M. Wilder</i> . . .	532
A Liberal Regimen of Treatment of Diabetes	<i>Henry J. John</i> . . .	537

Contents

v

Fatal Anuria, the Nephrotic Syndrome and Glomerular Nephritis as Sequels of Dermatitis of Poison Oak	<i>David A. Ryland</i>	548
Primary Carcinoma of the Liver	{ <i>Howard L. Holley</i> <i>Gray Pierson</i> }	561
Primary Carcinoma of the Liver	{ <i>Samuel D. Spatt</i> <i>David M. Grayzel</i> }	570
So-called Extrarenal Uremia. A Study of Twenty Cases	{ <i>Francis D. Murphy</i> <i>Bruno J. Peters</i> <i>Robert Carl Newman</i> }	574
Chemical Considerations in the Selection of Protein Hydrolysates	<i>Nelson F. Young</i>	586
Therapeutic Uses of Gamma Globulin		590
Acute, Severe Chest Pain with Fatal Termination		599
Visceral Neuropathy Complicating Diabetes Mellitus	{ <i>Jerome M. Swarts</i> <i>Leonard A. Stine</i> }	610
American Federation for Clinical Research—Abstracts of Papers Presented at the National Meeting Held in Atlantic City, May 4, 1948.		616
The Symposium on Syphilis—Editorial	{ <i>Harry Eagle</i> <i>J. R. Heller</i> }	629
Unknowns in the Biology of Syphilitic Infection	<i>Paul D. Rosahn</i>	631
Current Concepts of Immunity in Syphilis	<i>Harold J. Magnuson</i>	641
The Epidemiology of Syphilis. With Particular Reference to Contact Investigation.	<i>E. Gurney Clark</i>	655
Biologic False Positive Reactions in Serologic Tests for Syphilis.	<i>Hans Neurath</i>	670
Nationwide Results in the Treatment of Early Syphilis with Penicillin	<i>Frank W. Reynolds</i>	679
Penicillin Treatment of Early Syphilis.	<i>Evan W. Thomas</i>	687
Prevention and Treatment of Prenatal Syphilis	<i>Norman R. Ingraham, Jr.</i>	693
Penicillin in Benign Late and Visceral Syphilis	<i>Harold A. Tucker</i>	702
Significance of Spinal Fluid Findings in Neurosyphilis	<i>Bernhard Dattner</i>	709
Current Status of Penicillin Therapy in Neurosyphilis	<i>Harry C. Solomon</i>	712
Spontaneous Rupture of the Heart Due to Myocardial Infarction	{ <i>Franklin C. Massey</i> <i>William L. Drake, Jr.</i> }	775
Bundle Branch Block with Spontaneous Remission While Taking an Electrocardiogram	<i>Harry Ellis Canter</i>	780
The American Journal of Medicine Seminars on Hypertension	<i>Ephraim Shorr</i>	783
The Hemodynamic Response of Man to Nor-Epinephrine and Epinephrine and Its Relation to the Problem of Hypertension	{ <i>Marcel Goldenberg</i> <i>Kermit L. Pines,</i> <i>Eleanor de F. Baldwin</i> <i>David G. Greene</i> <i>Charles E. Roh</i> }	792

Effect of Tetraethylammonium in Arterial Hypertension	<i>A. Rune Frisk</i> <i>Sven Hammarström</i> <i>Henrik Lagerlöf</i> <i>Lars Werkö</i> <i>Gösta Björkenheim</i> <i>Alf Holmgren</i> <i>Yngve Larsson</i>	807
Effect of the Low Sodium Diet and the Rice Diet on Arterial Blood Pressure	<i>Benjamin Rosenberg</i> <i>Alfred E. Rosenthal</i> <i>Milton B. Rosenbluth</i>	815
Electrocardiographic Manifestations of Potassium Intoxication	<i>Harold J. Stewart</i> <i>Edward M. Shepard</i> <i>Eugene L. Horger</i>	821
Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances	<i>Robert Tarail</i>	828
Influence of the Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis	<i>Carl S. Nadler</i> <i>Samuel Bellet</i> <i>Mary Lanning</i>	838
Sponge Biopsy in Cancer Diagnosis	<i>Sidney A. Gladstone</i>	849
Use of Intermittent Positive Pressure Breathing Combined with Nebulization in Pulmonary Disease	<i>Hurley L. Motley</i> <i>Leonard P. Lang</i> <i>Burgess Gordon</i>	853
Psychosomatic Medicine. Its History, Development and Teaching	<i>Bernard B. Raginsky</i>	857
Assessment of Knowledge Concerning the Clinical Use of Protein Hydrolysates and Pure Amino Acid Mixtures	<i>D. P. Cuthbertson</i>	879
Feeble-mindedness or Pseudoretardation?		891
Diabetes, Fever of Unknown Origin and Coma		898
Acute Endocarditis Due to Staphylococcus Aureus Successfully Treated with Penicillin	<i>C. Maynard Guest</i> <i>Francis F. Harrison</i>	908
A Case of Infectious Mononucleosis with Jaundice and Thrombocytopenic Purpura	<i>A. Allen Goldbloom</i> <i>Abraham Liebersson</i>	912
Thrombophlebitis Migrans with Involvement of Both Lateral Sinuses	<i>Sedgwick Mead</i>	916

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The American Journal of Medicine

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Editorial

Retrospect and Prospect, 1948

WITH this issue The American Journal of Medicine enters upon its third year of publication. The occasion seems appropriate for a brief commentary on the problems of the preceding year and on the plans for the future.

A major editorial problem of the past year was how to deal with the flood of manuscripts submitted for publication. At the time the Journal was founded it was appreciated that additional vehicles for publication were needed but it was not anticipated that within so short a period the Journal would suffer an embarrassment of riches in this regard. Many manuscripts of real merit and interest had to be turned away. Despite this, the Journal has a large backlog of papers awaiting publication; of these the original investigations, studies of important new drugs, instructive clinical reports, and the like, are given precedence at the discretion of the editor. To expedite publication further and thus ensure current interest, the publishers have undertaken to increase the capacity of the Journal by adding thirty-two pages, as will have been noted in recent issues. This step and the continued fine format and typography are a warrant of the intention to maintain the highest standards.

The content of the Journal continues to reflect the editorial aims previously set forth: to aid in making generally available the results of sound clinical investigation, and to exploit the teaching opportunities of the Journal as an instrument for post-graduate medical instruction. By reporting both the research and teaching programs

of our large medical schools and clinics, the Journal seeks to reflect the main lines of current medical endeavor and faithfully to represent contemporary medical thought and practice.

As already indicated, there has been no difficulty in obtaining a sufficient number of experimental and clinical studies of high caliber and of the desired character and scope. These studies come from all parts of the country. Many are the work of younger men evincing great talent, capacity and thorough training; surely, an indication that American medicine is in a healthy and vigorous state, and a happy augury for the future.

Much time and thought were given to development of the teaching program of the Journal. The principal components of this program continue to be the various Conferences, which bring to the reader discussions of topics of current interest directly from the classrooms of university hospitals. The editors of these Conferences, the Cornell Conferences on Therapy, Columbia Combined Staff Clinics, Washington University Clinico-pathologic Conferences, Harvard Conferences on Psychosomatic Problems, have been unsparing of their time and energy to make these effective teaching exercises of sustained interest. The Journal is privileged to continue publication of the Conferences through the coming year.

Two series of seminars appeared in the pages of the Journal in the course of the past year, one on thromboembolism, the other on hypertension—timely subjects, dealt with fairly and authoritatively in their

manifold facets. The current issue brings the first of the new series, on the use of protein hydrolysates.

The November, 1947 and May, 1948 issues presented detailed symposia on allergy and on aviation medicine, respectively. For the coming year the Journal has scheduled symposia of similar high caliber on syphilis and poliomyelitis. Reviews and editorials on a variety of appropriate subjects have appeared and will continue to appear in each issue. For all these it has been possible to enlist the aid of authorities in their respective fields and they have given generously of their time and energy to strengthen the teaching program of the Journal.

To further the development of the younger societies for clinical investigation, the Journal has undertaken to publish the scientific proceedings of the American

Federation for Clinical Research, the Western Society for Clinical Research and the Southern Society for Clinical Research. These proceedings offer a varied program of much current interest and have proved a welcome addition to our pages.

It is most gratifying to the editorial board and to the publishers to note that these efforts have made for The American Journal of Medicine, even in this brief period, a place of respect and affection among the established medical journals of the country. The list of subscribers and readers has already reached a point ensuring stability of the Journal and maintenance of the present high standards in content and format. The Journal owes this success to the loyal support of its many friends and every effort is being made to justify and increase their confidence in its future.

ALEXANDER B. GUTMAN, M.D.

Antistreptolysin "O"*

A Study of This Antibody in Health and in Hemolytic Streptococcus Respiratory Disease in Man

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HEMOLYTIC streptococci responsible for nearly all primary infections, particularly of the respiratory tract in human beings, are members of a single serologic group designated by the letter "A."¹ The members of this group form at least two hemolysins.

One, streptolysin "S," is formed *in vitro* in the presence of serum. It is a very toxic, unstable substance and has been identified with the previously described Weld hemotoxin. The hemolysis of blood agar plates is caused by streptolysin "S." When injected into animals, this substance causes death in association with severe intravascular hemolysis. No rôle in human disease has been assigned to this product of the streptococci but it does stimulate the production of a neutralizing antibody in infected persons which has not been widely investigated.^{2,3,4}

Streptolysin "O" is the heat and oxygen labile hemolysin that is produced *in vitro* in serum-free broth.⁵ Its hemolytic action can be demonstrated only when it is in the reduced state. Differences of opinion exist as to its effect on living animals. Todd has shown that the lethal substance in filtrates of cultures of group A hemolytic streptococci when highly purified is heat and oxygen labile, indicating that it is streptolysin "O."^{6,7} This observation has been fully confirmed in this laboratory. Harris,⁸ on the

contrary, has described a heat and oxygen stable, lethal substance in somewhat similar preparations which Foley⁹ suggested might well be Dick toxin. Streptolysin O is a cardiotoxin for the frog heart,¹⁰ a leucocidin,¹¹ and is not the erythrogenic material.¹²

This toxin is not known to be etiologically responsible for any of the manifestations of the disease caused by hemolytic streptococci in man, but does stimulate the formation of an easily measurable antibody in infected human beings which has been extensively studied.¹³ Nearly all investigators have demonstrated that the serum concentration of antistreptolysin O is increased after infection by group A streptococci, in acute rheumatic fever and in glomerulonephritis, and that normal titers are the rule in rheumatoid arthritis and periarteritis nodosa.¹⁴⁻²²

Coburn^{23,24,25} has advanced the hypothesis that there is an intimate relationship between the nature of the antistreptolysin O response following streptococcal respiratory disease and the development of the rheumatic state. This argument has not been supported by all subsequent work^{26,27,28} although a similar observation has been made by Green.²⁹

Few of the earlier studies of the mechanics of the antistreptolysin O response involved serial antibody determinations in a large

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† This investigation was conducted under the auspices of the Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, Office of the Surgeon General, United States Army, Washington, D. C. Dr. Wesley W. Spink and Dr. Paul J. Boisvert participated in the clinical phases of this investigation.

group of infected individuals who were under close observation over considerable periods of time. This paper is the report of such an investigation conducted in military personnel.

CLINICAL MATERIAL

This report is based principally on a detailed study of 335 cases of group A hemolytic streptococcus sore throat in male military personnel who were admitted to a large station hospital. Patients were selected for inclusion in the study group on the basis of clinical and bacteriologic criteria that have been presented in great detail elsewhere.³⁰ Infection by group A hemolytic streptococci was established in 303 cases by the application of several immunologic procedures which were described in another report.³¹ Serial antibody determinations were available in 256 of these during the fourth week after the onset of acute respiratory infection. Most of the analyses in this paper will be based upon data collected from these 303 examples of proved streptococcal disease. Complete descriptions of the nature of the respiratory infections and of the suppurative and non-suppurative complications that frequently followed have been presented in a series of papers.^{30,32,33,34}

METHODS

Sera for antibody determinations were aseptically collected routinely on the second hospital day, again between the eighth and tenth, and between the twenty-first and twenty-eighth days of illness, and at weekly intervals thereafter in a selected group of cases.

The antistreptolysin* titers of the sera were measured by a method previously described.³⁵ The lysin was standardized against human sera of known antibody content obtained from Dr. Rebecca Lancefield. The method was later rechecked with rabbit serum containing 20,000 units per ml. which was supplied by Dr. E. W. Todd.

* The terms, streptolysin and antistreptolysin, as used throughout the remainder of the paper refer to streptolysin "O" and antistreptolysin "O."

No alteration in the originally obtained values was necessary.

A significant antistreptolysin response in this report has been defined as one in which the decrement of diluted serum in the system was 0.4 ml. or more. This corresponds to two dilution tubes as the method is performed in this laboratory.

THE ANTIBODY

Antistreptolysin is among the most satisfactory of all antibodies for laboratory study. The methods for its quantitation are simple and yield results that are more readily reproduced than those ordinarily obtained with immunologic procedures. Large numbers of sera may be titrated with ease. No loss of antibody content has been noted in sera stored aseptically at 2° to 3°c. over a period of two to three years.

The distribution of this immune substance among several of the plasma fractions of Cohn, as prepared from a single pool of plasma, is shown in Table 1. The antibody is, like many others, associated with the gamma globulin and is present in the various fractions in concentrations roughly comparable to the amount of this protein present in each. An increase in gamma globulin has been previously observed in association with an antistreptolysin response during recovery from group A hemolytic streptococcal infection.³⁶

Antistreptolysin crosses the placenta and appears in the fetal blood in amounts that are often greater than those present in the maternal blood.^{37,38} Great individual differences exist between various mothers and infants in the relative concentrations of antistreptolysin in the serum of the newborn child.³⁹ It is possible that these observations give information as to the permeability of the placenta to antibody, a subject of interest to students of Rh isoimmunization of the fetus.

The serum antistreptolysin concentration of human beings suffering from renal disease associated with the nephrotic syndrome is regularly low.^{40,41} Unpublished observations⁴¹ reveal that urinary proteins obtained

from such persons by dialysis and dehydration from the frozen state contain considerable amounts of this antibody. In four studied cases the daily excretion of antibody was 3,840, 1,250, 860 and 38 units per a twenty-four-hour period. The serum anti-

whole. No relationship between the duration of military service or the length of residence at the study post and the mean antistreptolysin titer was demonstrated. The data upon which this statement is based have been omitted.

TABLE I
CONCENTRATION OF ANTISTREPTOLYSIN "O" IN VARIOUS PLASMA FRACTIONS (COHN)

	Plasma Fraction							
	I	II	III ²	IV ¹	IV ³⁻⁴	IV ⁶	IV ⁷	V
Concentration of gamma globulin* (per cent)	10	95	27	1	0	0	5.5	0
Concentration of antistreptolysin "O" in units per Gm. of dry protein	100	6,600	660	100	0	0	100	0

* As determined by electrophoretic analysis.

streptolysin titers in each instance were 50, 24, 12 and less than 5 units per ml., respectively. The amount of antibody in the urine was roughly proportional to the serum concentration. The low serum antistreptolysin titers in the presence of heavy proteinuria are presumably the result of loss of this substance in the urine.

Interesting investigations into the nature of the process leading to inactivation of streptococcus hemolysin by antistreptolysin may be suggested but none have been undertaken. Unpublished studies made in this laboratory have demonstrated that a non-hemolytic formalin toxoid prepared from streptolysin will neutralize the anti-hemolytic effect of the antibody with the same facility as the untreated lysin in the oxidized or reduced state.

ANTISTREPTOLYSIN "O" TITERS IN HEALTH

It has been shown previously that the range of antistreptolysin titers of sera from healthy human beings varies with the age^{26,38,42} and geographical area of residence of the subjects.⁴³ The antibody levels of sera obtained from 588 young male soldiers at the onset of an acute respiratory illness have been analyzed. It is believed that these titers are representative of those in the population of the study group as a

The pre-military residences of the members of the study group have been compared with the antistreptolysin titer and the data summarized in Table II. The mean antibody levels varied greatly from area to area, being lowest in the Southwest and Southeast and highest in the Middle West and Far West. Statistical analysis reveals that Zones 7 and 11 varied significantly from the group as a whole. A small number of additional comparisons presented at the bottom of the table demonstrate that the differences between the mean titers in several areas are also significant.

The range of titers in this group of 588 males of military age, whose pre-military residences had been distributed over the whole United States, is presented in Table III (Columns 7 and 8). Data derived from three additional investigations of somewhat similar scope in adults and children are included. The first was conducted one year after the work described in this paper among a similar population in a military establishment (Columns 9 and 10).⁴⁴ The subjects for the second study in 1934 were young civilian adults living in various parts of the United States (Columns 11 and 12).⁴³ The third includes healthy children and older adults who were studied in the

TABLE II
DISTRIBUTION OF ANTISTREPTOLYSIN "O" TITERS IN HEALTHY HUMAN BEINGS

Antistrep- tolysin Titer (units per ml. of serum)	Present Study											
	Children Age 1.5-3 years		Children Age 5-12 years		Adults Age 40-60 years		Military Personnel		Lemon and Hamburger		Coburn and Pauli	
	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total
	<12		238		33		117		91		104	
Mean titer	17 *	94.4	23	22.7	27	61.3	94	16.0	28	14.5	0	0.0
12 or less	0	0.0	11	10.9	13	29.5	128	21.8	66	34.1	89 †	23.3
50	0	0.0	9	8.9	1	2.3	82	13.9	30	15.8	160	42.1
100	0	0.0	7	6.9	2	4.5	120	20.4	34	17.6	63	16.5
125	0	0.0	15	14.8	1	2.3	97	16.4	28	14.5	42	11.1
166	1	5.5	6	5.9	0	0.0	42	7.1	5	2.5	15	3.9
250	0	0.0	11	10.9	0	0.0	12	2.0	2	1.0	9	2.3
333	0	0.0	6	5.9	0	0.0	8	1.4	0	0.0	3	0.8
500	0	0.0	6	5.9	0	0.0	6	1.0	0	0.0	0	0.0
625	0	0.0	4	3.9	0	0.0	0	0.0	0	0.0	0	0.0
833	0	0.0	3	2.9	0	0.0	0	0.0	0	0.0	0	0.0
1,250	0	0.0										
Total	18	100.0	101	100.0	44	100.0	589	100.0	193	100.0	381	100.0

* Titers less than 12 units in 16
† Values less than 50 units per ml. included here

TABLE III
RELATIONSHIP OF PRE-MILITARY RESIDENCE TO THE ANTISTREPTOLYSIN "O" TITER

Zone*	Region	No. of Cases	Mean Anti- streptolysin Titer (units per ml.)	Standard Error	P—Mean All Cases
1	New England	56	110	±14	>.5
2	New York	66	105	±13	.4
3	North Atlantic	61	127	±11	.4
4	Middle Atlantic	37	99	±17	.4
5	Border	49	108	±15	>.5
6	Southeast	45	96	±14	.2
7	Southwest	40	82	±11	<.01
8	Great Lakes	137	130	±9	.2
9	Middle West	47	150	±19	.1
10	Rocky Mountain	7	110	±24	>.5
11	Far West	43	150	±11	<.01
All Cases		588	116	±4	

* Zone 1: Me., N. H., Vt., Mass., Conn., R. I.
Zone 2: N. Y.
Zone 3: Pa., N. J., Del., Md.
Zone 4: Va., N. C., S. C.
Zone 5: W. Va., Ky., Tenn.
Zone 6: Ga., Fla., Ala., Miss., La.; Ark.
Zone 7: Tex., Okla., Ariz., N. Mex.
Zone 8: Ohio, Ind., Ill., Mich., Wis., Minn.
Zone 9: N. Dak., S. Dak., Nebr., Kan., Iowa, Mo.
Zone 10: Mont., Idaho, Wyo., Col., Utah
Zone 11: Calif., Wash., Ore.

Zone 9 compared with Zone 7 P = <.01
Zone 9 compared with Zone 6 P = .02
Zone 9 compared with Zone 4 P = .05
Zone 8 compared with Zone 7 P = .01
Zone 8 compared with Zone 6 P = .04
Zone 3 compared with Zone 7 P = <.01

San Francisco area between 1940 and 1947 (Columns 1, 2, 3, 4, 5 and 6).

The results obtained in the three young adult groups, remote from one another in time and space, are quite similar. (The values of Lemon and Hamburger⁴⁴ are lower because hemolytic streptococcus carriers were excluded.) Antistreptolysin titers in children under three years of age were very low. Between the ages of five and fifteen there was a sharp increase in the antibody concentrations, the mean titer for all subjects in this group being nearly twice as great as in young adults.

The percentages of young men whose antibody level was 100 units per ml. or less were 51.7, 64.4 and 65.3 for the three groups, whereas 11.5, 3.5, and 7.0 per cent had antistreptolysin titers of 250 units per ml. or more. After forty years of age the levels were uniformly low.

Comment. The concentration of antistreptolysin in the sera of healthy human beings varies with the age and geographic area of residence of the population under study. Antibody levels are very low after the first months of life, rise constantly through the first decade and then decline with advancing age. These results are in accord with the established frequency of occurrence of hemolytic streptococcal respiratory infection in the several age groups.

The antistreptolysin titers of persons living in southern United States, where the incidence of streptococcal disease is low, are less than in those residing in the north where infection by these organisms is a common event. These observations demonstrate that a correlation exists between the frequency of infection by group A streptococci in a group of human beings and the range and mean antistreptolysin titers of their sera.

It is not presently possible to draw any finite conclusions in regard to the relationship between the absolute rate of infection and the mean antistreptolysin titer. Because the measurement of this antibody is extremely simple and because the method can be well standardized, a program could be

readily planned which should give satisfactory information in regard to the relative incidence of group A hemolytic streptococcal respiratory infection in various populations.

Statistically adequate numbers of sera should be collected from individuals of comparable age groups in various areas of this country and elsewhere during the same season of the year. The early fall, when streptococcal infections are occurring infrequently in most communities in the Northern Hemisphere, would be an appropriate time. The sera could be shipped to a central laboratory for titration since antistreptolysin is quite stable.

A study of this sort by an agency of national or international scope would yield information of the greatest value in regard to the relative incidence of group A hemolytic streptococcal infections throughout the area under investigation. Mote and Jones have demonstrated the usefulness of such a technic in estimating the rate of occurrence of infection by these organisms in six groups of human beings in a variety of environments.²⁶

Important inferences in regard to the ecology of group A hemolytic streptococci and the epidemiology of infection caused by them may be drawn from these data. The sera of 85 per cent of older children and young adults contains 50 or more units of antistreptolysin per ml. Since antibody levels during the first two years of life are much lower than this, it is evident that clinical or inapparent infection by hemolytic streptococci has occurred in nearly every person residing in the United States. These facts emphasize the universality of infection by these organisms.

Any attempt to establish a "normal" range of values for the titer of antistreptolysin in man is meaningless unless the age and geographic area of the study group is defined. An antibody level of 250 units or more in a young adult strongly suggests that a hemolytic streptococcal infection has been a relatively recent event. Different standards must be applied in infancy, childhood,

middle and old age. The data of Mote and Jones²⁶ may be used for the first twenty years of life in New England and certain of the information contained in this report for the United States as a whole and for the San Francisco area.

summarized graphically in Figure 1. The antibody levels at the onset of the acute streptococcal respiratory infection and those obtained eight to ten and twenty-one to twenty-eight days later are recorded. Therapeutic regimens, including the administra-

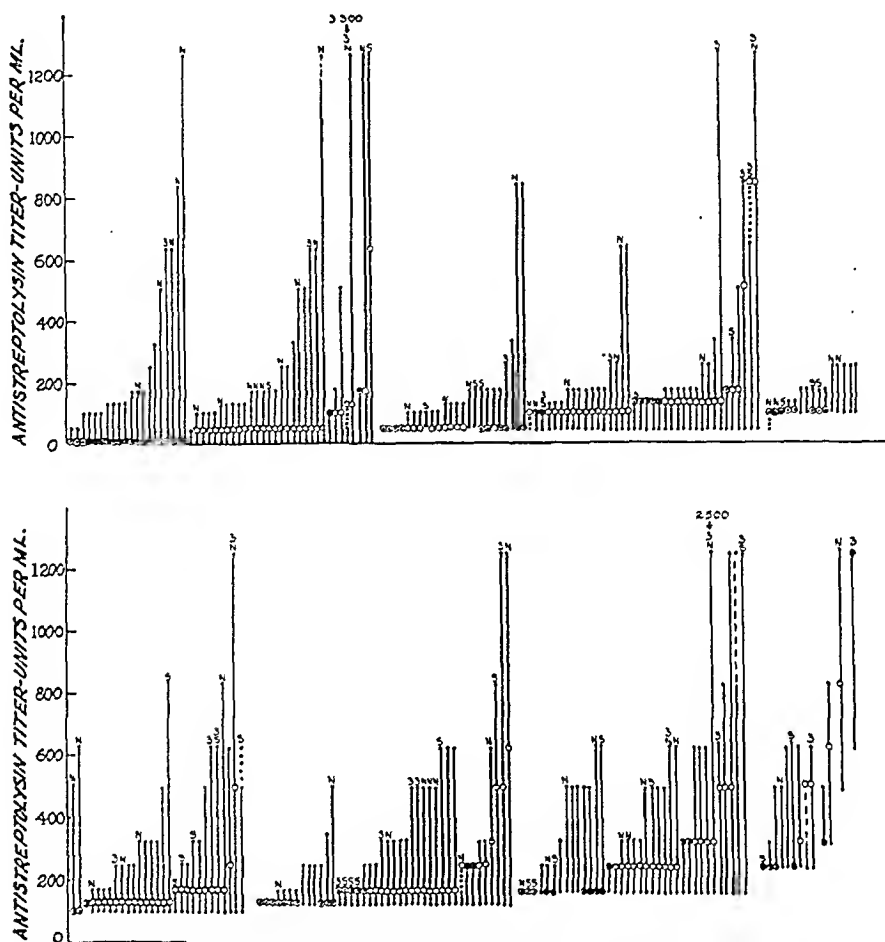


FIG. 1. Lower dot indicates initial antibody level; circle indicates antibody level on eighth to tenth day of illness; upper dot indicates antibody level during fourth week of illness; superscript "N" indicates a non-suppurative complication; superscript "S" indicates a suppurative complication; superscript "3" indicates infection by a streptococcus of type 3.

Isolated determinations of the antistreptolysin titer should be interpreted with the greatest caution when evaluating the relationship of hemolytic streptococcal infection to various pathologic states.

ANTIBODY MECHANICS

Most of the essential information derived from the study of the antistreptolysin response in 256 cases of proved group A hemolytic streptococcus infection has been

tion of penicillin, sulfadiazine and sodium salicylate in various amounts and combinations, were instituted in many of the patients. These procedures have been ignored throughout this paper since previous analyses demonstrated that none greatly altered the natural history of the disease or the antibody response which accompanied it.^{33,45,46}

Certain generalizations may be made from the data. An increase in antibody

occurred in approximately 95 per cent but was significant as defined in this paper in only 87.5 per cent of these patients. The accuracy of the method for determination of the antibody is exemplified by the fact

only 9 per cent of cases in whom any response was noted.

Great individual differences were observed in the magnitude of the antistreptolysin response as indicated by antibody

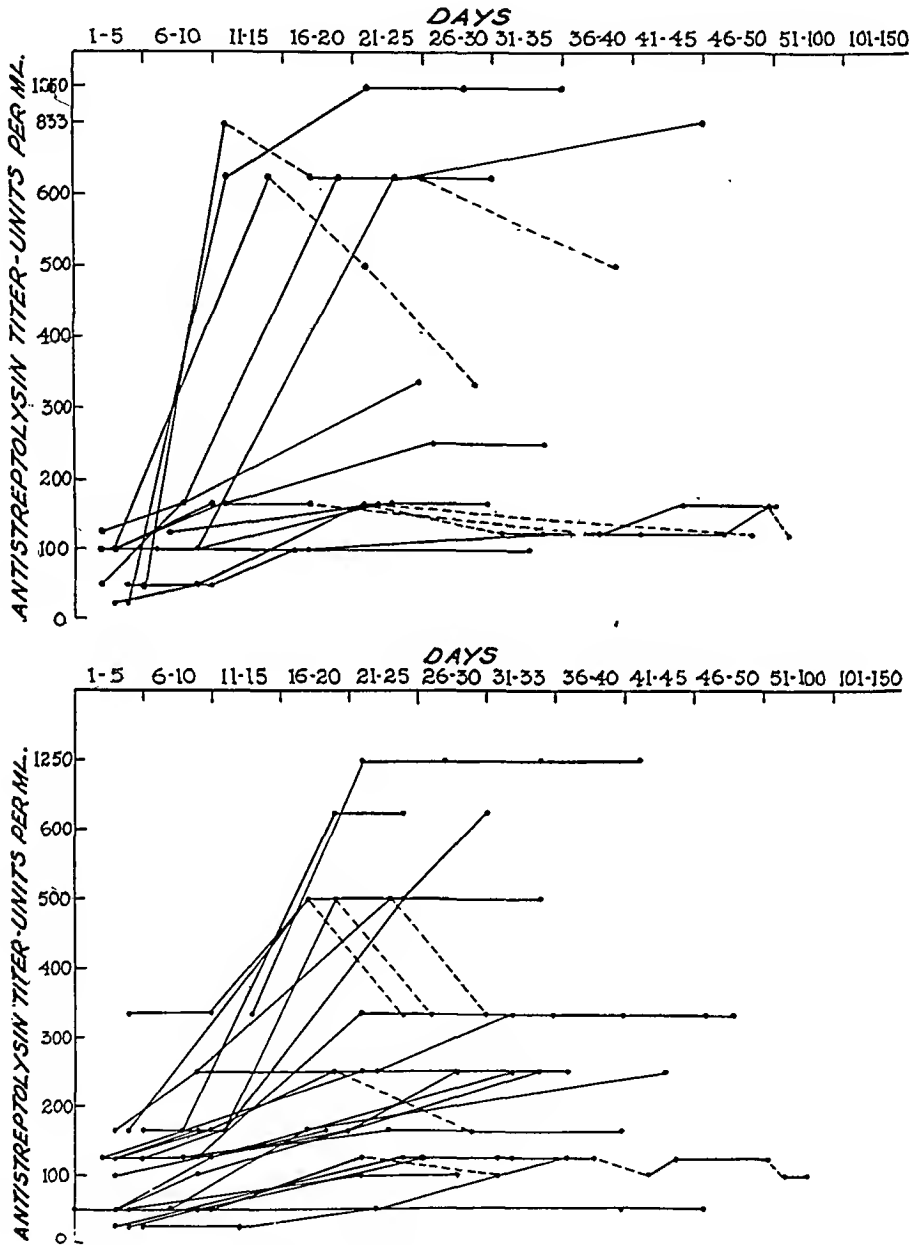


FIG. 2. Lower panel: uncomplicated cases; upper panel: suppurative complications.

that a fall in antistreptolysin titer from that obtained at the onset was never detected.

An increment in antibody concentration was discovered in approximately 55 per cent and was significant in 43 per cent of all patients by the tenth day of illness. The maximum titer was reached at this time in

levels present during the fourth week which were probably nearly maximal in most cases. (Figs. 2 and 3.) The attainment of very high titers at this time was most often associated with infection by a streptococcus of type 3 or with the development of a suppurative or non-suppurative complica-

tion. Fifty-two of seventy-nine, or 66 per cent, of patients in whom the peak antistreptolysin titer was 500 or more units per ml. fell into one of these three categories whose total number made up only about 40 per cent of all cases. Titers as great as

tion will be the subject of additional comment later in this paper.

Only a few of the uncomplicated cases were followed by means of serial antibody determinations after the fourth week. The results obtained as well as those in patients

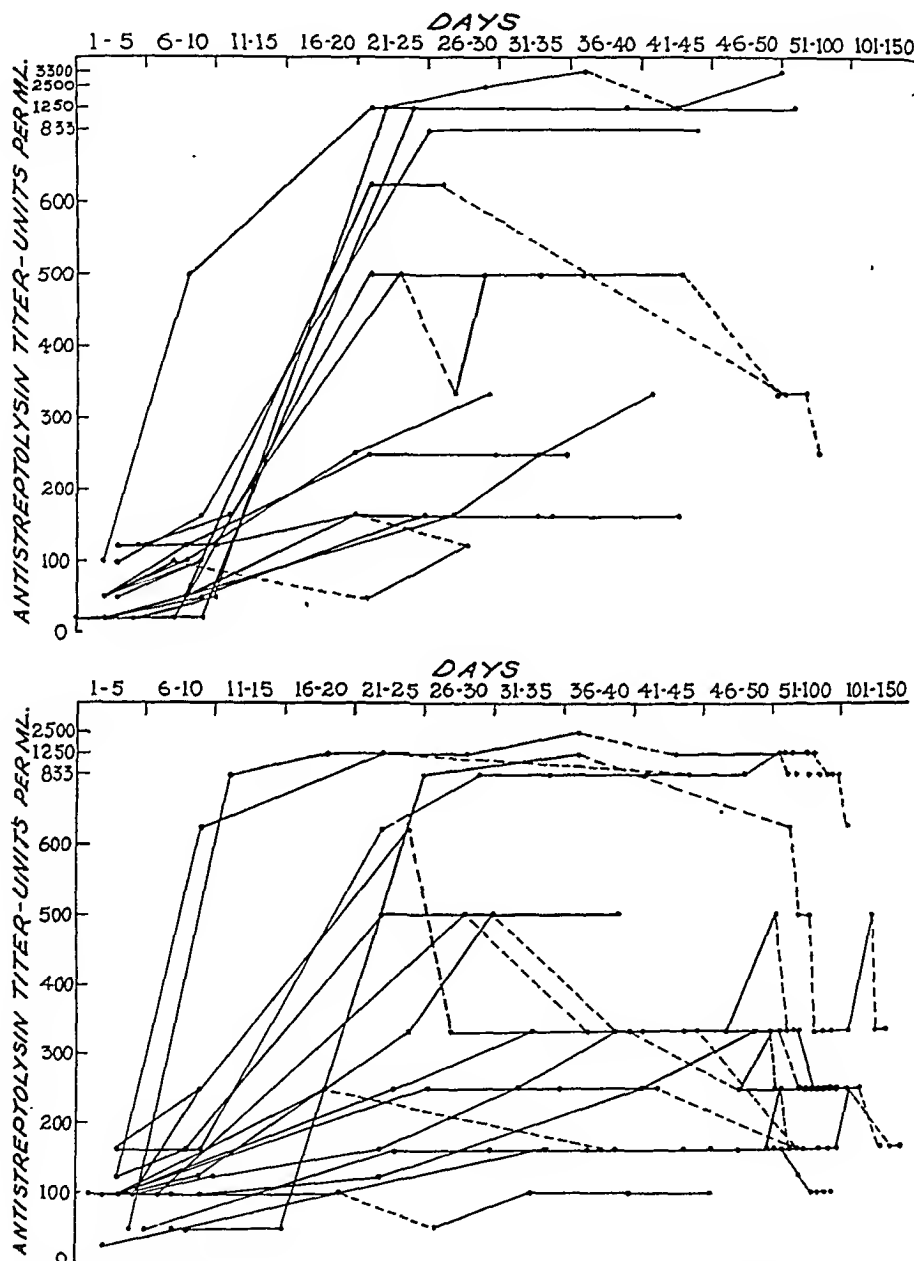


FIG. 3. Upper panel: non-suppurative complications—carditis and late fever; lower panel: non-suppurative complication—arthritis.

this were attained by 53 per cent of patients in whom a non-suppurative complication supervened, but only by 23 per cent of uncomplicated infections not caused by type 3. This potentially important observa-

who developed a suppurative complication or a non-suppurative disorder, in which the manifestations were arthritis, fever or carditis, are displayed graphically in Figures 2 and 3. These figures again demonstrate the

quantitatively more vigorous production of antistreptolysin in association with suppurative and non-suppurative complications.

The maximum antibody level was attained by the end of the fourth week in a large majority of the patients followed after

lysin formed by patients whose titer at the onset varied from 12 to 250 units was comparable.

Information in regard to the apparent antistreptolysin mechanics in relationship to the dilution system used for the measure-

TABLE IV
RELATIONSHIP BETWEEN NATURE OF THE CLINICAL DISEASE AND ANTISTREPTOLYSIN TITER DURING CONVALESCENCE FROM HEMOLYTIC STREPTOCOCCUS SORE THROAT

Antistreptolysin Titer at Follow-up †	Uncomplicated Cases, Day of Follow-up Study*			Suppurative Complications, Day of Follow-up Study*			Non-suppurative Complications, Day of Follow-up Study*					
	30-40	40-50	50+	30-40	40-50	50+	30-40	40-50	50-60	60-70	70-80	80 †
Unchanged.....	10	3	0	7	2	0	18	20	10	7	7	2
Significant increase.....	1	1	0	0	0	0	5	0	0	0	0	0
One tube increase.....	5	1	0	1	0	0	11	1	0	0	0	0
Significant decrease.....	1	0	1	0	0	0	2	0	4	2	1	2
One tube decrease.....	2	0	2	2	1	0	4	4	5	3	2	3
Total.....	19	5	3	9	4	0	40	25	19	12	10	7

* Patients not tabulated after that period in which a significant fall in antibody was first observed.

† As compared with titers during the fourth week.

this period, irrespective of the presence or absence of complications. The development of arthritis or other non-suppurative disorder was not associated with a slow or delayed antistreptolysin response.

The antibody concentrations, after reaching a peak, were usually maintained for a considerable period of time. Table IV summarizes the information in regard to this point. After the fiftieth day significant declines in the antistreptolysin titer occurred frequently but were not observed in many patients followed for two or more months.

One of the authors has previously stated⁴⁷ that the fold increase in antistreptolysin in human beings is greater following infection by group A hemolytic streptococci if the initial antibody titer is low than if it is high. This point of view has been criticized⁴⁸ and it has been suggested that the total production of antibody is probably similar at any initial level. Table V confirms this suggestion. The mean quantity of antistrepto-

ment of the antibody is presented in this table. It will be observed that an increment in antibody of greater absolute magnitude is required as the initial level becomes higher if a significant response is to be detected. A progressive fall occurred in the frequency of significant increments in antistreptolysin in this group of patients as the antibody titers at the onset of the infection increased. A two-tube response was observed in 100 per cent of patients whose initial level of antistreptolysin was very low and in only 70 to 80 per cent of those in whom large amounts of antibody were present early in the disease. Since the mean production of antibody at all levels is similar, it is clear that the failure to demonstrate a significant response in certain cases is almost entirely the result of the technic used in the measurement of the antibody. The results are similar when any, other than significant, antibody response is considered (last three columns of Table V).

Comment. Certain details of the mechanics of antistreptolysin response in a large number of proved group A hemolytic streptococcus respiratory infections in young adults have been presented.

An increase in antibody was observed in nearly all cases by the fourth week after the

RELATIONSHIP OF INITIAL ANTISTREPTOLYSIN "O" TITER TO THE NATURE OF THE CLINICAL DISEASE

A previous study has indicated that the concentration of antistreptolysin in the serum of patients at the onset of hemolytic streptococcal respiratory disease bears no

TABLE V
RELATIONSHIP BETWEEN INITIAL ANTISTREPTOLYSIN "O" TITER AND FREQUENCY AND MAGNITUDE OF ANTIBODY RESPONSE

Initial Antistreptolysin Titer (units/ml.)	Ml. of Diluted Serum in System	No. of Cases	Mean Increase in Antibody (units/ml.)	Increment Required for Significant Response (units/ml. *)	Significant Responses		Increment Required for Any Detectable Response (units/ml.)	No Response	
					No.	%		No.	%
12	.8	51	277	38	51	100.0	38	0	0.0
50	.2	62	216	75	57	91.9	50	4	6.4
100	1.0	44	244	66	39	88.8	25	2	4.5
125	.8	41	271	125	29	70.7	41	3	7.3
166	.6	38	377	167	30	78.7	84	4	10.5
250	.4	9	269	250	6	66.6	83	1	11.1

* A decrease of .4 ml. or more of diluted serum in the system.

onset of the illness and was usually maximal at this time. Frequently a response had occurred by the eighth to tenth day and was often significantly large but rarely maximal. The mean magnitude of the increase in antibody was shown to have been comparable at all initial levels of antistreptolysin. The dilution system used in the measurement of this immune substance resulted in a progressive decline in the incidence of significant responses as the titer of antibody at the onset of the illness became larger.

Great individual differences in the magnitude of the antistreptolysin response were exhibited by different patients. The largest increments in antibody were observed in men infected by strains of type 3, or in those in whom suppurative or non-suppurative complications supervened.

Little information was obtained in regard to the persistence of antistreptolysin in the serum after the first month. Decrements in antibody concentration were not uncommon during the following thirty days but were not observed in many patients.

relationship to the natural history of the acute illness.⁴⁹ This observation has been fully confirmed during the investigation described in this report. The initial antistreptolysin titer could not be correlated with the degree of abnormality of physical signs, height or duration of fever or the initial or follow-up erythrocyte sedimentation rate. The data on which this statement is based have been omitted. Normal or moderately elevated total leukocyte counts were associated with higher mean antistreptolysin levels than were high counts when antibody determinations and clinico-pathologic observations were made early in the acute illness. (Table VI.)

The differences between the two lower categories of total leukocyte counts and the third (13,000 to 15,999) and fourth (16,000 or more) are significant (P equals .01 to .02). Inspection of the distribution curves of the antibody levels from which these means were derived suggests that the variations just described may not be valid biologic correlations.

The amount of antistreptolysin present in the serum at the onset of acute hemolytic streptococcus sore throat has been compared with the frequency of development of suppurative and non-suppurative complications.^{32,33,34} (Table VII.) The distribution of

TABLE VI
RELATIONSHIP BETWEEN INITIAL ANTISTREPTOLYSIN TITER
AND TOTAL LEUKOCYTE COUNT

Initial Total Leukocyte Count (cells per cu. mm.)	No. of Cases	Mean Anti-streptolysin Titer (units per ml.)	Standard Error
9,000 or less.....	69	104	± 10
10,000 to 12,999.....	82	104	± 10
13,000 to 15,999.....	68	73	± 7
16,000 or more.....	75	93	± 6

and mean titers in patients who recovered uneventfully and in those in whom otitis media, peritonsillar abscess and sinusitis were diagnosed were similar.

The late appearance of arthritis, fever and carditis, as exemplified by the presence of an abnormal electrocardiogram, has been regarded as a manifestation of a common pathologic process.^{32,34} The mean initial antistreptolysin titer in forty individuals in whom one of these complications appeared during convalescence was lower than the value obtained in uncomplicated cases and in those with suppurative complications. Further analysis demonstrates that antibody levels were very low in patients who developed late fever and carditis and were high in arthritics. Four persons in the latter group had initial antistreptolysin titers of less than 100 units per ml. The involvement of the joints was minimal in three, and the fourth suffered a series of reinfections by strains of hemolytic streptococci of different serologic types before arthritis became manifest.

Comment. If streptolysin "O" has a rôle in the pathogenesis of any of the manifestations of the acute suppurative phase of group A hemolytic streptococcus sore throat, a correlation should exist between the concentration of neutralizing antibody (anti-

streptolysin "O") at the onset of the illness and the severity or extent of those manifestations of the disease process caused by this toxin. This and previous investigations have established the fact that no such relationship can be demonstrated. Further-

TABLE VII
RELATIONSHIP BETWEEN INITIAL ANTISTREPTOLYSIN "O"
TITER DURING THE ACUTE PHASE OF STREPTOCOCCAL
SORE THROAT AND DEVELOPMENT OF COMPLICATIONS

Antistreptolysin O Titer (units/ml.)	No. of Cases*	Uncomplicated	Suppurative Complications	Non-suppurative Complications			
				Arthritis	Late Fever	Carditis	Total
12 or less	51	39	2	1	6	3	10
50	71	56	6	3	3	3	9
100	47	30	8	8	1	0	9
125	48	36	5	3	2	2	7
166	34	26	5	2	0	1	3
250	13	10	2	1	0	0	1
333	3	2	0	0	1	0	0
500	2	2	0	0	0	0	0
625	1	1	0	0	0	0	0
Mean titer		98	109	107	70	67	79
Total cases	270	202	28	18	13	9	39

* Twenty-one cases in which a variety of probable or possible non-suppurative complications occurred²⁴ have been omitted.

more, certain streptococci that produce abnormally large amounts of hemolysin do not cause disease differing in any respect from that resulting from infection by the strains forming less of this substance.³³ These observations suggest that it is proper to dismiss this substance from the armamentarium of toxins produced by group A hemolytic streptococci that are known to affect human tissues directly.

Arthritis and late fever, with or without carditis, and the latter complication alone have been regarded as non-suppurative complications of hemolytic streptococcus respiratory infection and the pathogenesis of all has been believed to be similar. An immunologic difference between arthritic and non-arthritic poststreptococcal disease has been demonstrated.⁵⁰ Involvement of the joints was much more frequently associated with the presence initially or development during convalescence of a precipitating antibody reacting with a component of acid extracts of group A streptococcal cells.

The present investigation has revealed another dissimilarity between these disorders. The initial antistreptolysin titers were higher in patients who were later to develop arthritis than in those in whom fever, with or without carditis or carditis alone, were manifestations of the complication. This relationship was particularly striking if only severe or moderately severe arthritic cases were considered.

The number of patients with complications in these three categories is small but the results become more impressive when it is realized that the initial antistreptolysin titer was less than 100 units per ml. in 66 per cent of uncomplicated and 68 per cent of cases in which non-arthritic, non-suppurative complications appeared. Antibody concentrations as small as this were never discovered in the early sera collected from patients who developed marked arthritis unless reinfection by new types of hemolytic streptococci occurred (one case).

This observation adds weight to the argument previously offered³² which stated that all forms of poststreptococcal non-suppurative disease were the result of an immunologic reaction, possibly involving sensitization by preceding contact with the organism. The suggestion was made that non-arthritic disorders, frequently followed an isolated infection by a single type, but that the production of arthritis probably required multiple, relatively closely spaced infection by hemolytic streptococci leading to an advanced degree of hypersensitivity. The moderately elevated antistreptolysin titers discovered in men at the onset of streptococcal disease followed by arthritis indicate that these patients had undergone infection by these organisms more recently than the remaining patients in whom the joints were not involved.

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO NATURE OF CLINICAL DISEASE

The data obtained from the study of 256 of the 303 proved cases of group A hemolytic streptococcus sore throat were analyzed to

determine the relationship between the frequency and magnitude of antistreptolysin response and the nature of the acute illness and complications which often followed it. Patients were selected for inclusion in the group only if follow-up antibody determinations were made during the fourth week after the onset of infection.

Data obtained from the whole group of 256 cases were used for the determination of the frequency of antibody response. The mean antistreptolysin increase was calculated from the results in 237 patients in whom any increment in antibody occurred. In several instances this was not a significant response. Analyses were made with infections caused by streptococci of type 3 included and excluded. The latter procedure was performed because the magnitude of antistreptolysin response associated with infection by organisms of this type was usually exaggerated and, in part, obscured well defined trends in magnitude of antibody response which will be described.

Acute Suppurative Disease. Close relationship between certain manifestations of the acute suppurative phase of hemolytic streptococcus sore throat and the absolute magnitude but not the frequency of antistreptolysin response has been demonstrated. A progressive increase occurred in the mean amount of antistreptolysin formed as the maximum temperature became greater (Table VIII) or more prolonged. (Table IX.)

The differences were highly significant statistically when maximum temperature was considered. Significance was obtained in the analysis pertaining to duration of fever only when the categories including patients with a very short febrile illness were compared with those in whom elevated temperatures had persisted for six or more days.

The magnitude of antistreptolysin response varied in an irregular way (Table X) with the initial erythrocyte sedimentation rate, but patients whose initial rate was less than 20 mm. per hour formed significantly less antibody than did the group as a

TABLE VIII

RELATIONSHIP OF MAXIMUM TEMPERATURE TO FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE

Maximum Temperature	Frequency of Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response							
	No. of Cases	Significant Response		All Cases with Any Increase	Mean Increase (units/ml.)	Standard Error	All Cases Except Type 3 with Any Increase	Mean Increase (units/ml.)	Standard Error	P* 98.6-99.9	P* 100.0-100.9
		No.	%								
Afebrile-99.9	17	13	81.3	16	132	±29	16	132	±29		
100.0-100.9	22	19	86.4	20	193	±43	17	151	±39		
101.0-101.9	52	44	84.6	46	273	±34	43	257	±30	<.01	.2
102.0-102.9	57	51	89.5	55	312	±43	50	275	±41	<.01	.05
103.0 and greater	108	97	89.8	100	312	±36	93	295	±37	<.01	.05-.02
Total	256	224	87.5	237	282	±20	219	260	±19		

* Including type 3

TABLE IX

RELATIONSHIP BETWEEN DURATION OF FEVER AND FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE

Duration of Fever (days)	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response					
	No. of Cases	Significant Response		All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody		
		No.	%	No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error
0 to 1	48	39	81.3	46	232	± 32	42	214	± 31
2	63	55	87.3	56	230	± 28	53	224	± 29
3	67	61	91.0	66	300	± 48	57	249	± 47
4	38	33	86.8	32	255	± 40	31	220	± 40
5	15	13	86.6	13	410	±114	13	410	±114
6 or more	25	23	92.0	24	418	± 86	23	388	± 76
All cases	256	224	87.5	237	282	± 20	219	260	± 20

Statistical comparisons of mean increases (type 3 cases included)

P of 0-to-1 compared with 5 equals .2-.1

P of 0-to-1 compared with 6 or more equals .05

P of 2 compared with 5 equals .2-.1

P of 2 compared with 6 equals .05

TABLE X

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO INITIAL ERYTHROCYTE SEDIMENTATION RATE

Initial Erythrocyte Sedimentation Rate (mm./hr) Westergren	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response						
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody			
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error	P* Mean All Cases
		No.	%							
9 or less	22	20	90.9	19	182	±32	18	181	±33	<.02 .05
10 to 19	51	44	86.2	47	208	±33	43	187	±28	
20 to 29	51	41	80.4	46	321	±47	41	296	±46	
30 to 39	44	41	93.5	41	251	±33	39	237	±33	
40 to 49	33	30	90.9	30	376	±68	29	349	±65	
50 and more	48	41	85.4	47	323	±64	42	261	±66	
Total	249	217	87.2	230	282	±21	212	259	±20	

* P greater than .1 omitted; type 3 included.

TABLE XI

RELATIONSHIP BETWEEN INITIAL TOTAL LEUKOCYTE COUNT AND FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE

Total Initial Leukocyte Count/cu. mm.	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response					
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody		
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error
		No.	%						
9,000 or less	51	43	84.3	46	282	±45	43	259	±43
10,000 to 12,999	73	66	90.3	66	315	±45	59	281	±45
13,000 to 15,999	59	48	81.3	54	232	±35	51	202	±30
16,000 and more	70	64	91.4	68	286	±35	63	285	±38
Total	253	221	87.4	234	281	±20	216	258	±20

whole. The frequency of response was similar in all categories. No relationship between the maximum initial total leukocyte count and the incidence or size of the antistreptolysin response was discovered. (Table xi.)

cases but the variations were not statistically significant. (Table xiii.)

Non-suppurative Complications. A considerable number of hemolytic streptococcus respiratory infections in this study group initiated pathologic processes apparently

TABLE XII

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO FOLLOW-UP (4TH WEEK) ERYTHROCYTE SEDIMENTATION RATE

Follow-up Erythrocyte Sedimentation Rate (mm./hr.) Westergren	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response						
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody			
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error	P* Mean All Cases
		No.	%							
9 or less	121	102	84.3	108	190	± 16	102	185	± 16	< .01
10 to 19	53	48	90.5	51	271	± 42	46	217	± 35	
20 to 29	29	25	86.2	27	326	± 52	25	299	± 51	
30 to 39	23	20	86.9	22	398	± 83	19	388	± 85	.1
40 to 49	11	11	100.0	11	375	± 127	11	375	± 127	
50 or more	19	18	94.7	18	602	± 133	16	567	± 142	.05-.02
Total	256	224	87.5	237	282	± 20	219	260	± 19	

* P greater than .1 omitted; type 3 included.

The follow-up (fourth week) erythrocyte sedimentation rate was closely correlated with the amplitude of the antistreptolysin response. (Table xii.) Rapid rates at this time were associated with large increases in antibody and the reverse. This phenomenon appears to be associated with the presence of many complicated cases in the group with rapid erythrocyte sedimentation rates at follow-up examination.

Suppurative Complications. The course of twenty-eight cases of hemolytic streptococcus sore throat was complicated by the development of suppurative disorders. Peritonsillar abscess, otitis media and sinusitis were observed. The frequency of antistreptolysin response was slightly greater in these patients and the amount of antibody produced was larger than in uncomplicated

of a non-suppurative nature.³⁴ Clinical manifestations of these disorders were arthritis with or without fever or carditis (rheumatic fever), late fever with or without carditis, carditis without fever or arthritis, and pneumonitis with or without carditis. Eighteen less clearly defined pathologic states, including late lymphadenitis and prolonged abnormality of the erythrocyte sedimentation rate in the absence of clinical evidence of disease, are segregated in a separate category.

The data summarized in Table xiii reveals that the frequency and magnitude of antistreptolysin response were greater in the presence of all forms of non-suppurative poststreptococcal disorders than in uncomplicated cases.

The variation in total antibody produc-

tion was of statistical significance only in the groups including patients suffering from late fever and miscellaneous disorders. When all non-suppurative disorders were considered together, a similar significant statistical result was obtained.

(Case 7),³⁴ and was insufficiently great to be significant in additional examples of arthritis, late fever and carditis (one case in each category). These and related complications occurred in many other patients in whom the increment in antistreptolysin was

TABLE XIII
RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO COMPLICATIONS OF HEMOLYTIC STREPTOCOCCUS SORE THROAT

Type of Complication	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response in All Cases with Any Increase in Antibody			P-Mean Uncomplicated Cases
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	
		No.	%				
Uncomplicated	169	131	72.5	156	210	± 18	
Suppurative complications	28	23	82.1	25	330	± 67	.1
All non-suppurative complications	59	54	91.5	57	434	± 58	.01
Arthritis	18	16	88.9	17	366	± 85	.1
Late fever	13	12	92.4	13	516	±109	.02
Carditis	7	6	85.6	7	344	±170	.5
Pneumonitis	3	3	100.0	3	367		
Other non-suppurative complications	18	17	94.4	20	450	±120	.05
All cases	256	206	80.7	238	282	± 20	<.01

The data presented in Figure 1 demonstrate the vigorous formation of antistreptolysin by many patients in whom non-suppurative complications were observed. Figures 2 and 3 illustrate the course of the antibody response in greater detail and show clearly that peak levels were obtained at a comparable time (fourth week) after the onset of the initial acute hemolytic streptococcus respiratory infection in complicated and uncomplicated cases. The same information is summarized in another form in Table iv.

Although excess production of antistreptolysin by patients in whom non-suppurative complications have supervened is not statistically significant in every category, it is an impressive phenomenon which requires explanation. No antistreptolysin response whatever occurred in one of the most severely ill patients with arthritis

only moderately large (Fig. 1) and the maximum titer was less than 200 units per ml. A marked increase in this antibody is not essential therefore in the pathogenesis of these disorders.

It has been demonstrated previously that the frequency and magnitude of antistreptolysin response are related to the severity of the initial suppurative phase of hemolytic streptococcus sore throat. Certain manifestations of acute illness have been analyzed with regard to the subsequent development of complications. (Table xiv.) Inspection of the data reveals that the maximum temperature was lower, the febrile illness of definitely shorter duration and the initial erythrocyte sedimentation rate much less rapid in uncomplicated cases. The average respiratory infection which was to be followed by a suppurative or non-suppurative complication was more severe

than were those in which convalescence was uneventful.

COMMENT

No correlation has ordinarily been demonstrable between the severity of various

TABLE XIV
RELATIONSHIP OF SEVERITY OF INITIAL ILLNESS TO THE DEVELOPMENT OF COMPLICATIONS

Category	Uncomplicated		Suppurative Complications		Non-Suppurative Complications	
	No.	%	No.	%	No.	%
Duration of fever (in days)						
Afebrile to 1 day	35	22.4	2	8.0	8	14.0
2 days	39	25.0	3	12.0	14	24.5
3 days	45	28.8	6	24.0	14	24.5
4 days	19	12.2	7	28.0	9	15.8
5 days	6	3.8	2	8.0	5	8.8
6 or more days	12	7.7	5	20.0	7	12.3
Maximum temperature						
98.6 to 99.9° F.	15	9.6	1	4.0	0	0.0
100.0 to 100.9° F.	16	10.3	2	8.0	2	3.5
101.0 to 101.9° F.	31	19.9	6	24.0	10	17.5
102.0 to 102.9° F.	30	19.2	6	24.0	19	33.3
103.0° F. and higher	64	41.0	10	40.0	26	45.6
Initial erythrocyte sedimentation rate (Westergren)						
9 or less	18	11.8	0	0.0	1	1.8
10 to 19	38	25.0	1	4.1	9	16.4
20 to 29	35	23.0	3	12.5	8	14.5
30 to 39	25	16.4	5	20.8	11	20.0
40 to 49	16	10.5	6	25.0	8	14.5
50 and up	20	13.2	9	37.5	18	32.7

infectious diseases and the magnitude of antibody response which was associated with them. A previous investigation failed to discover such a relationship in group A hemolytic streptococcus sore throat.⁵⁰ The results of the present study differ in that the mean amplitude of the antistreptolysin response was progressively greater as the acute streptococcal respiratory infection became more severe. This phenomenon was most striking when maximum temperature was used as a measure of the severity of the illness, but was quite apparent when comparisons were made between the duration of fever or the initial erythrocyte sedimentation rate and antibody response.

Another analysis derived from these data has demonstrated that the frequency and magnitude of antistreptolysin response may be a function of the serologic type of the infecting hemolytic streptococcus.³¹ This was not responsible for the variations just described since the severity of the illness caused by strains of the various types was similar.³³ Comparable differences in the size of the antistreptolysin response were observed in a monotype food-borne epidemic of hemolytic streptococcus sore throat in which the factor of strain differences could be excluded as a cause for the variations in production of this antibody.⁴⁷ Clinical data were inadequate in that study to permit an analysis of antibody mechanics in relationship to the nature of the disease.

The fact that a relationship exists between the severity of acute streptococcal illness and the formation of antistreptolysin was less important and interesting than the demonstration of a similar correlation between the presence or absence of non-suppurative complications and the average magnitude of antibody response. Coburn^{23,24} has previously stated that this was the case, but subsequent investigations and a preliminary analysis of present data⁵⁰ failed to support his position. However, complete statistical evaluation of information obtained during the study confirms the work of this investigator, as does that of Green.²⁹

It is clear that the mean production of antistreptolysin was greater in patients selected on clinical grounds as examples of late non-suppurative complications of hemolytic streptococcal disease than in those in whom prompt and uneventful recovery occurred. Patients were segregated into groups on the basis of the development of arthritis, late fever, pneumonia, carditis or another probable non-suppurative disorder. Excess antistreptolysin formation was demonstrated in all categories. This is to be contrasted with the different situation which was discovered when certain antibacterial precipitating antibodies were studied in these same patients.⁵⁰ These substances

were demonstrated with unusual frequency only when arthritis supervened.

The relationship between the augmented production of antistreptolysin in the presence of complications, particularly of the non-suppurative type, demands elucidation which is not possible from the data at hand. The suggestion has been made that these disorders are the result of immunologic reactions, possibly of the anaphylactic type, which are harmful to the tissues. If this be the case, some fraction or product of the hemolytic streptococcus must be the sensitizing antigen and this substance must be common to many types or strains of these organisms. Streptolysin is such a substance and the observations reported here suggest that it and its antibody may be intimately related to the pathogenesis of the non-suppurative poststreptococcal complications. It may be proposed that this toxin is, indeed, the sensitizing antigen itself and that these disorders arise in human beings who form excess amounts of its antibody following infection leading to hypersensitivity of susceptible tissues. A cogent objection to this hypothesis is the fact that arthritic and non-arthritic poststreptococcal disease occurred in individuals in whom no or only minimal increments in antibody were observed and in whom the total concentration of the immune substance remained low. This observation should be contrasted with those of Coburn²⁴ who maintained that hemolytic streptococcal respiratory infection was not usually followed by the development of a non-suppurative complication in the absence of a large antistreptolysin response.

The possibility must also be considered that the increased production of antistreptolysin in persons who have developed a poststreptococcal complication simply mirrors a generally increased immunologic hyper-reactivity on the part of these patients which led to the development of sensitivity states in which the streptolysin-antistreptolysin system had no rôle. Study of the precipitating antibody previously mentioned did not confirm this suggestion.

Elsewhere³² it has been noted that a large number of clinical and inapparent reinfections by streptococci of new types occurred in patients who later developed non-suppurative complications and it was possible that these multiple exposures to the infectious agent had resulted in excessive antibody production by these persons. Examination of antibody mechanics in relation to intervals between infections fails to support this hypothesis in more than a few instances. Neither was there an unusually great number of infections by types known to stimulate the formation of large amounts of antistreptolysin.³¹

It has been noted above that the magnitude of the antistreptolysin response was related to the severity of the acute streptococcal disease, and evidence was presented which showed that the frequency of occurrence of severe initial illnesses was high among those men who later developed a non-suppurative complication. It is logical to assume, therefore, that the excess antibody production which was demonstrated in complicated cases was a function of the nature of the inciting infectious processes rather than the result of any of the other mechanisms suggested as explanations of this phenomenon.

No completely satisfactory explanation for the association of non-suppurative poststreptococcal complications and the excessive formation of antistreptolysin has been offered. It is imperative that further investigation of this phenomenon be conducted, since the elucidation of the pathogenesis of these important disease states must be one of the principal goals of all studies of hemolytic streptococcal infection. Methods utilizing fully dialyzable synthetic culture media are now available which permit the preparation of the extracellular products of the streptococcus in a highly purified form.¹⁰ These should be studied for the purpose of devising technics for the separation of streptolysin from the erythrogenic and other substances formed by group A streptococci. Valuable information as to the effect of streptolysin on human tissues

will be obtained when this has been accomplished.

CONCLUSIONS

Antistreptolysin "O" is an immune substance which neutralizes streptolysin "O" *in vitro*. It is contained in the gamma globulin fraction of human serum. Its concentration in the sera of healthy persons and its formation after infection in young adults by group A hemolytic streptococci has been studied. The data have been presented and described in several categories, each of which has been the subject of special comment in the body of the paper.

The amount of this substance in sera obtained from healthy persons varies with the geographic area of residence of the subjects and their age. Antibody levels are very low through the second year of life, rise rapidly through the first decade and then decline. The presence of a wide range of antistreptolysin titers in health indicates that single determinations of the antibody must be interpreted with caution in studies of the etiology of various human diseases.

The mechanics of antistreptolysin response in large numbers of carefully studied examples of proved group A hemolytic streptococcus sore throat have been described. It was noted that an increase in this antibody occurred regularly following infection by these organisms. The amplitude of the response varied from patient to patient but the peak level was reached by the fourth week after the onset of acute illness in nearly all cases.

No relationship between the initial antistreptolysin titer and the nature of the acute suppurative phase of hemolytic streptococcus sore throat was demonstrated. The amount of antibody was moderately increased at this time in patients who later developed arthritis.

A definite correlation between the magnitude of antistreptolysin response, severity of the initial illness and the later development of non-suppurative complications was demonstrated.

These observations and those described

in another paper establish immunologic differences between uncomplicated group A hemolytic streptococcus respiratory infection and that which initiates a non-suppurative disorder. An exaggerated mean antistreptolysin response occurred in all clinical categories of the latter group. In addition, the antistreptolysin titer at the onset of the initial streptococcal illness was somewhat higher, and antibacterial precipitating antibodies were present with unusual frequency in patients who later developed arthritis. These facts demand an explanation since one of the primary goals of all studies of hemolytic streptococcal disease must be the elucidation of the pathogenesis of these important late complications of which rheumatic fever is the best known example.

Various interpretations of the phenomenon of excessive antibody formation in association with the appearance of non-suppurative disorders were offered but none was entirely satisfactory. Either the streptolysin-antistreptolysin or the X-anti-X antibody systems may be directly responsible for the hypersensitivity that is presumed to cause non-suppurative poststreptococcal disorders. On the other hand, the abnormal production of these antibodies may mirror an exaggerated immunologic hyper-reactivity of human beings in whom these disease states develop. In the latter case the sensitizing fraction or product of the organism is one whose significance has not been appreciated or it has not yet been discovered.

The preparation of highly purified streptolysin "O," separated from the erythrogenic material and other products of the hemolytic streptococcus, and the study of its properties and effects upon human tissues is a problem urgently requiring investigation.

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Streptococcal Fibrinolysin (Streptokinase)*

A Study of This Substance and Its Antibody in Group A Hemolytic Streptococcus Sore Throat†

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TILLET and Garner in 1933 described a substance formed by hemolytic streptococci which was able to induce the liquefaction of human plasma clots *in vitro*. It has usually been designated as streptococcal fibrinolysin.^{1‡} More recent investigation has demonstrated that this product of streptococcus is not a true lytic substance but is an enzyme activator or kinase, which activates the precursor of a protease which is present in normal human plasma.²⁻⁵ The active enzyme will liquefy not only fibrin but other proteins as well. The suggestion has been made that the term "streptococcal fibrinolysin" be abandoned and that this substance be known as streptokinase.⁶

Large amounts of an antiprotease may appear or be present in plasma.⁷ Fibrinolysin will not induce plasma clot lysis under these circumstances. This situation is observed most frequently in the presence of certain acute infections in man and in animal plasma.

Earlier work revealed that an antibody appeared during convalescence from hemolytic streptococcal infections which was able to inhibit the clot liquefying properties of fibrinolysin. This immune substance was absent in nearly all healthy human beings

‡ The information available on this subject in 1938 has been reviewed in detail.¹ No specific reference to the literature before that date will be made in this paper.

and present in many persons suffering from acute rheumatic fever^{1,8,9,10} and hemorrhagic nephritis.

Recent studies have correlated the production of fibrinolysin with the serologic groups and types of hemolytic streptococcus and it has been demonstrated that an immunologically similar factor is formed members of groups A, C and G.^{11,12} Strains of group A of various types, epidemic within the armed forces during the recent war, varied strikingly in their ability to make fibrinolysin *in vitro* and to stimulate the production of neutralizing antibody in infected human beings.^{13,14}

Methods for the measurement of anti-fibrinolysin, based upon the time required for a broth culture of a standard strain of hemolytic streptococcus to induce lysis of the plasma clot of the individual under study, are relatively crude and do not express the concentration of antibody in quantitative terms.^{1,15} A more precise method has been described recently.¹⁶

This paper is a report of a detailed study of a large number of cases of group A hemolytic streptococcus sore throat in military personnel. Serial measurements of the antifibrinolysin titer were made and the ability of the infecting streptococcus to form fibrinolysin *in vitro* was determined. The results were correlated with the natural history of the clinical disease.

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† This investigation was conducted under the auspices of the Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, Office of the Surgeon General, U. S. Army, Washington, D. C. Dr. Wesley W. Spink participated in the clinical phase of this study.

CLINICAL MATERIAL

This report is based principally on a detailed study of 335 cases of group A hemolytic streptococcus sore throat in male military personnel who were admitted to a large station hospital. Patients were selected for inclusion in the study group on the basis of clinical and bacteriologic criteria that have been presented in great detail elsewhere.¹⁷ Infection by group A hemolytic streptococci was established in 303 cases by the application of several immunologic procedures which were described in another report.¹⁸ Serial antibody determinations were available in 243 of these during the fourth week after the onset of the acute respiratory infection. Most of the analyses in this paper will be based upon data collected from these 243 examples of proved streptococcal disease. Complete descriptions of the nature of the respiratory infections and of the suppurative and non-suppurative complications that frequently followed have been presented in a series of papers.¹⁹⁻²³

METHODS

Plasma for antibody determinations was aseptically collected routinely on the second hospital day, again between the eighth and tenth and between the twenty-first to twenty-eighth days of illness, and at weekly intervals thereafter in certain cases. The antifibrinolysin concentration of plasma was determined by the method of Tillet and Garner¹ as modified by Boisvert.¹⁰ A prolongation of clot lysis time of eight or more hours has been used as a measure of significant antibody response for the purpose of this study.

The *in vitro* production of fibrinolysin by group A hemolytic streptococci isolated from the respiratory passages of these patients was determined and recorded as follows: Streptococci were grown in neopeptone veal infusion broth for eighteen hours at 37°C. One-half ml. of the resultant culture, including the streptococcal cells,

was added to .2 ml. of a standard* plasma and .8 ml. of normal saline. The mixture was clotted with .25 ml. of .25 per cent solution of calcium chloride. The time required for complete clot lysis was determined by frequent observation during incubation of the preparations in a water bath at 37°C. A number was assigned to each result as follows:

Plasma Clot Lysis Time	No. in Vitro
0 to 30 minutes	6
30 to 60 minutes	5
1 to 3 hours	4
3 to 8 hours	3
8 to 24 hours	2
No lysis in 24 hours	1

The mean of the *in vitro* numbers for all of the studied strains of hemolytic streptococci obtained from any individual patient has been used as a measure of the ability of the infectious agent in that patient to produce fibrinolysin *in vitro*.

FIBRINOLYSIN PRODUCTION

One hundred ninety-six patients in whom evidence of infection by only a single type was discovered were segregated into various categories on the basis of clinical and clinicopathologic study, and the mean production of fibrinolysin *in vitro* by the etiologic agent in each was determined. No correlation was discovered between *in vitro* production of fibrinolysin by the infecting hemolytic streptococcus and the severity of the initial illness as indicated by the height or duration of fever, the total leukocyte count or the initial erythrocyte sedimentation rate. The data upon which this statement is based have not been presented.

Certain details of the relationship between *in vitro* production of fibrinolysin by the infecting streptococcus and the development of complications are presented in Table I. It will be observed that suppurative and non-suppurative complications followed

* Plasma from three healthy persons was pooled. A clot prepared from this material was lysed in fifteen minutes or less by cultures of strains of streptococci known to produce large amounts of fibrinolysin.

disease caused by organisms of every degree of lytic potency and that the mean production of lytic substance in uncomplicated cases and in every type of complication was comparable.

protein. Available evidence does not permit a decision as to whether very large amounts of the antibody, antifibrinolysin, or antiprotease have been concentrated in this fraction.

TABLE I

RELATIONSHIP BETWEEN THE *in vitro* PRODUCTION OF FIBRINOLYSIN BY THE INFECTING HEMOLYTIC STREPTOCOCCUS AND THE DEVELOPMENT OF SUPPURATIVE AND NON-SUPPURATIVE COMPLICATIONS

<i>In vitro</i> Fibrinolysin Production. No. of Infecting Streptococcus	Uncomplicated	Suppurative Complications	Non-suppurative Complications				
			All	Arthritis	Carditis	Late Fever	Other
1	11	2	3	1	0	1	1
2	10	2	4	1	0	0	3
3	25	0	6	3	0	2	1
4	31	3	4	2	1	1	0
5	21	3	5	0	1	1	3
6	44	6	13	4	1	3	5
Total	142	16	35	11	3	8	13
Mean <i>in vitro</i> number	4.2	4.3	4.2	4.0	5.0	4.2	4.2

ANTIFIBRINOLYSIN

The Antibody. Relatively little information is available in regard to the properties of antifibrinolysin since techniques for its quantitation have not been satisfactory and because antiprotease, rather than antibody, has frequently been detected by the methods used.

The apparent distribution of this substance among the several plasma fractions of Cohn from a single pool of plasma is shown in Table II. The antibody was

TABLE II

	II	III-2	IV-1	IV-3-4	IV-6	IV-7	V
Concentration of gamma globulin (per cent) . . .	95	27	1	0	0	5.5	0
Concentration of antifibrinolysin in units (Kaplan) per Gm. of dry protein	26,500	30	0	0	0	30	0

measured by the method described by Kaplan.¹⁶ An antifibrinolytic substance was discovered only in fractions containing gamma globulin and was present in very large amounts in fraction II, which was composed almost entirely of this type of

Relationship of Initial Antifibrinolysin Titer to Nature of Clinical Disease. The antifibrinolysin titer of the serum at the onset of acute group A hemolytic streptococcus sore throat as expressed in clot lysis time in hours was compared with various features of the clinical disease. The concentration of antibody of 88 per cent of cases was very low (lysis time of three hours or less). (Table III.) In others the antiprotease of acute febrile illness interfered with the test. For these reasons this phase of the analysis was unsatisfactory and most of the data have not been presented. There was no relationship between the initial antifibrinolysin titer and the subsequent development of suppurative and non-suppurative complications. (Table III.)

Antibody Mechanics. The essential data derived from the study of the antifibrinolysin response in 243 cases of proved group A hemolytic streptococcus sore throat have been summarized in Table IV. Antibody levels at the onset of infection and those obtained eight to ten and twenty-one to twenty-eight days later are recorded. Therapeutic regimens, including the administra-

tion of penicillin, sulfadiazine and sodium salicylate in various amounts and combinations, were instituted in many of these patients. These procedures have been ignored throughout this paper since previous analyses indicated that none greatly altered

in only twenty-eight, or 11.4 per cent, of all cases at this time. In ten of these, or 4.1 per cent of the whole group, clot lysis resistance was decreased by the eighth to tenth day, indicating that antiprotease, rather than antibody, was being detected.

TABLE III

RELATIONSHIP BETWEEN INITIAL ANTIFIBRINOLYSIN TITER AND THE DEVELOPMENT OF SUPPURATIVE AND NON-SUPPURATIVE COMPLICATIONS

Initial Plasma Clot Lysis Time (in hr.)	Uncomplicated		Suppurative Complications		Non-suppurative Complications					
					All		Arthritis	Carditis	Late Fever	Other
	No.	Per Cent	No.	Per Cent	No.	Per Cent				
0 to 1	133	82.1	24	92.3	45	81.8	15	4	11	15
1 to 3	10	6.2	0	0.0	3	5.4	1	0	0	2
3 to 8	3	1.8	0	0.0	1	1.8	0	1	0	0
8 to 24	2	1.2	1	3.8	2	3.6	0	0	1	1
24	14	8.6	1	3.8	4	7.3	0	2	0	2

TABLE IV

ANTIFIBRINOLYSIN RESPONSE IN 213 CASES OF GROUP A HEMOLYTIC STREPTOCOCCUS SORE THROAT

Initial Plasma Clot Lysis Time (in hr.)	Total Cases		Cases Unchanged Throughout*		Cases with Increase or Decrease in Clot Lysis Time of Any Magnitude										
					Observations at 8 to 10 Days						Observations during 4th Week				
					Cases Not Stud- ied (days)	Clot Lysis Time (in hr.)					Clot Lysis Time (in hr.)				
	No.	Per Cent	No.	%†		8-10	0-1	1-3	3-8	8-24	24+	0-1	1-3	3-8	8-24
0 to 1	202	83.1	103	50.9	6	56	6	3	6	22	1	21	11	8	58
1 to 3	13	5.3	1	7.7	2	2	1	1	1	5	0	1	1	4	6
3 to 8	4	1.6	0	0.0	1	0	2	0	1	0	0	0	1	1	2
8 to 24	5	2.0	0	0.0	2	0	0	1	1	1	0	1	0	1	3
24+	19	7.8	10	52.6	0	3	0	1	3	2	2	1	2	1	3

* No change in clot lysis time during four weeks of observation.

† Per cent of cases of this initial antibody level.

the natural history of the disease or the antibody response that accompanied it.^{20,24}

Inspection of the table reveals that the initial plasma of 88.4 per cent of all cases contained only minimal amounts of antibody (clot lysis time of three hours or less). Increased resistance to clot lysis was present

A definite increase in antibody concentration had occurred by the eighth to tenth day in thirty-four, or 15.8 per cent, of 215 cases in which the initial antifibrinolysin level was low. During the fourth week a significant response was discovered in approximately 35 per cent of these patients.

An increase of clot resistance to lysis of a degree not believed to be significant was noted at this time in thirty-four additional cases. No alteration whatever in the lysis time was observed in 104 patients.

mately 16 per cent of cases by the eighth to tenth days, and an additional 19 per cent by the fourth week of illness. Significant decrements in antibody concentration were first observed after the sixth week and had

TABLE V
RELATIONSHIP OF HEIGHT AND DURATION OF FEVER TO
FREQUENCY OF SIGNIFICANT ANTIFIBRINOLYSIN RESPONSE

	Maximum Temperature—°F.					Duration of Fever in Days				
	98.6 to 99.9	100.0 to 100.9	101.0 to 101.9	101.0 to 102.9	103 +	0-1	2	3	4	5 or more
Number of cases	16	20	49	54	104	45	60	67	37	34
Number of significant antifibrinolysin responses	2	5	14	19	38	11	15	22	15	15
Percentage of significant antifibrinolysin responses	12.5	25.0	28.6	35.2	36.5	24.4	25.0	32.8	40.5	44.1

Certain of the other patients in whom increased amounts of antibody or anti-protease were present initially (clot lysis time of three or more hours) also exhibited a response. The number of such cases was small and interpretation of the results difficult. They will not be discussed in detail.

Serial antifibrinolysin determinations were available after the fourth week in a few cases, most of which were examples of non-suppurative poststreptococcal complications. Not one of the fifteen patients in whom maximal resistance to clot lysis was present during the fourth week exhibited a decrease in antibody concentration by the fortieth day after the onset of acute streptococcal respiratory infection. Occasional significant decrements in antibody level were observed at irregular intervals in the smaller group followed through the twelfth week. At this time clot lysis occurred in less than three hours in approximately 40 per cent of these patients.

Comment. The concentration of serum antifibrinolysin was very low in 90 per cent of young men at the onset of group A hemolytic streptococcus sore throat. Evidence of antiprotease activity was demonstrated at this time in a very few cases. A significant antibody response occurred in approxi-

been detected in 40 per cent of a very small group followed through the twelfth week.

RELATIONSHIP OF FREQUENCY OF ANTI-FIBRINOLYSIN RESPONSE TO NATURE OF CLINICAL DISEASE

The data obtained from a study of 243 of 303 proved cases of group A hemolytic streptococcus sore throat were analyzed to determine the relationship between the frequency of antifibrinolysin response and the nature of the acute illness and complications which often followed it. Patients were selected for inclusion in the group only if follow-up antibody determinations were made during the fourth week after the onset of infection.

Acute Suppurative Disease. A definite relationship between certain manifestations of the acute suppurative phase of hemolytic streptococcus sore throat and the frequency of significant antifibrinolysin response has been demonstrated. Such an increase in antibody occurred more often as the maximum temperature became greater or more prolonged. (Table v.) The differences were most striking when height of fever was considered. No correlation between antibody response and initial leukocyte count or erythrocyte sedimentation rate was noted.

Suppurative Complications. The course of twenty-six of these cases of hemolytic streptococcus sore throat was complicated by the development of suppurative disorders. Peritonsillar abscess, otitis media and sinusitis were observed. The frequency

of the poststreptococcal state since these disorders appeared in many persons in whom increased resistance to clot lysis was at all times absent. (Table vi.) This important fact is further emphasized by the data presented in Table vii in which is

TABLE VI
RELATIONSHIP OF THE PRESENCE OF SUPPURATIVE AND NON-SUPPURATIVE COMPLICATIONS TO THE FREQUENCY OF SIGNIFICANT ANTIFIBRINOLYSIN RESPONSE

	Type of Case						
	Uncomplicated	Suppurative Complications	Non-suppurative Complications				
			All	Arthritis	Late Fever	Carditis	Other
Number of cases.....	162	26	55	16	12	7	20
Number of cases with plasma clot lysis time of less than 60 minutes throughout illness.....	64	8	11	4	2	3	2
Number of significant antifibrinolysin responses..	41	12	25	7	7	1	10
Percentage of significant antifibrinolysin responses	25.3	46.1	45.5	43.7	53.3	14.3	50.0

of significant antifibrinolysin response was greater in these patients (46.1 per cent) than in uncomplicated cases (25.3 per cent) and the difference is of statistical significance.

Non-suppurative Complications. A considerable number of hemolytic streptococcus respiratory infections in this study group initiated pathologic processes, apparently of a non-suppurative nature. Clinical manifestations of these disorders were arthritis with or without fever or carditis (rheumatic fever), late fever with or without carditis and carditis without fever or arthritis. Twenty less clearly defined pathologic states are segregated in a separate category.

The data summarized in Table vi reveal that the frequency of significant antifibrinolysin response was greater in the presence of all forms of non-suppurative poststreptococcal disorders except carditis than in uncomplicated cases. These differences are of statistical significance when the values obtained for the total complicated group are compared with those for the uncomplicated subjects.

An increase in antifibrinolysin is not essential in the pathogenesis of the phe-

summarized the results obtained when the antifibrinolysin content of sera obtained during the course of hemolytic streptococcus sore throat complicated by arthritis (rheu-

TABLE VII
ANTIFIBRINOLYSIN RESPONSE IN EIGHT CASES OF POST-STREPTOCOCCAL ARTHRITIS IN WHICH THE ANTIBODY WAS STUDIED BY THE KAPLAN METHOD

	Case Number							
	1	2	3	4	5	6	7	8
Types of infecting streptococcus.....	19	19	26	36	36	36	36	46
Increase in serum antifibrinolysin in units per ml.....	575	11	483	58	47	0	0	1975
Increase in dilution tubes.....	6	1	2	3	2	0	0	8
Maximum serum antifibrinolysin titer in units per ml.....	625	36	900	83	83	<25	<25	2100

matic fever) was determined by the more precise Kaplan method.¹⁶ An increase in antibody occurred in six of eight cases but was not of great magnitude in three in

whom the peak antifibrinolysin titer was never greater than 58 units. Of greater interest were two subjects who developed arthritis in the absence of measurable (less than 25 units per ml.) serum antifibrinolysin at any time during the course of the illness.

Earlier in this section it was demonstrated that the frequency of the antifibrinolysin response was related to the severity of the initial suppurative phase of hemolytic streptococcus sore throat. It should be recalled at this time that evidence presented elsewhere²⁵ indicated that non-suppurative complications were more likely to follow severe than mild forms of this disease.

COMMENT

Group A hemolytic streptococci produce a substance, usually called fibrinolysin, which is able to activate a protease present in normal human plasma and thus to induce liquefaction of human plasma clots *in vitro*. Earlier investigators suggested that the invasiveness of these organisms might be enhanced by the elaboration of this substance *in vivo* with a dissolution of the fibrin deposits that normally participate in the localization of infections.¹ This hypothesis may be correct if infections other than those of the upper respiratory tract are considered.

The results of the present study showed that none of the clinical manifestations of acute group A hemolytic streptococcal sore throat could be related to the *in vitro* production of fibrinolysin by the infecting organism. Furthermore, disease of great severity and suppurative and non-suppurative complications were observed in patients whose infection was caused by strains (notably of type 3) the *in vitro* lytic activity of which was slight.

An antibody often appears in the serum of human beings during convalescence from hemolytic streptococcal infection that neutralizes the enzyme activating property of this bacterial product. Investigation of this immune substance has been hampered by the relatively crude methods available for

its quantitative estimation. Recent studies have indicated that the frequency of significant antibody response in a group of unselected hemolytic streptococcal respiratory infections is largely dependent on the ability of the infectious agents to form fibrinolysin.

The data obtained from the study of a large number of cases of group A hemolytic streptococcus sore throat have been pooled and considered together in the present analysis of antibody response. The lytic and antibody stimulating properties of the isolated streptococci varied greatly with their serologic type. It was believed, however, that useful information might be obtained from this analysis since it has been shown in previous reports^{17,20,21} that the natural history of the disease was not related to the serologic type of causative streptococcus (except for rash formation), and it has just been demonstrated that a similar situation prevails in regard to *in vitro* production of fibrinolysin.

An increment in antifibrinolysin of significant magnitude occurred in 16 per cent of all cases by the eighth to tenth day, and in an additional 19 per cent by the fourth week after the onset of acute streptococcal illness.

A more severe acute respiratory illness, as indicated by the height and duration of fever, was associated with a significantly greater frequency of antifibrinolysin response. Similarly, the incidence of antibody response was greater in the presence of suppurative and non-suppurative complications than in uncomplicated cases. A similar observation was made by certain earlier investigators.¹ In an extensive study Mote and Jones also demonstrated a greater frequency of antifibrinolysin response when hemolytic streptococcal infection was followed by the development of arthritis than when it was not. The differences described were not great.⁸

In two previous reports^{25,26} it has been noted that an antibacterial precipitating antibody appeared or was present initially more often in the serum of persons whose

acute streptococcal illness was followed by the development of arthritis and that the magnitude of the increase in antistreptolysin "O" was greater in association with all forms of non-suppurative poststreptococcal disorders. These pathologic states may be the result of hypersensitivity of the anaphylactic type and it was suggested that the presence of abnormal concentrations of these antibodies might be directly responsible for an increased tissue sensitivity in patients in whom such complications develop. Under these circumstances the X-antigen or streptolysin "O" could be regarded as the sensitizing substance *per se*.

On the other hand, it was proposed that the increased production of antibodies by persons who had developed a poststreptococcal complication simply mirrored a generally increased immunologic hyper-reactivity on the part of these patients which led to the development of sensitivity states in which the X-anti-X antibody or the streptolysin "O"-antistreptolysin "O" systems had no specific rôle. It was also emphasized that non-suppurative complications most often followed the more severe initial infections that were associated with an exaggerated antistreptolysin response, and also that these disorders appeared in certain patients in whom the serum concentrations of these antibodies was always low.

An analogous situation has now been demonstrated in regard to fibrinolysin and it becomes increasingly apparent that the excessive formation of antibodies by persons who develop the disorders of the poststreptococcal state is indeed the result of a non-specific immunologic hyperreactivity. This mechanism seems particularly applicable to the explanation of the augmented production of antistreptolysin and anti-fibrinolysin which has been described. It does not clearly elucidate the phenomena observed in relationship to the anti-X antibody since this substance was demonstrated in abnormal amounts only in the presence of arthritis and since joint disease appeared with unusual frequency in persons

in whom the antibody was present at the onset of acute respiratory infection as well as in those in whom it appeared later.

Further speculation as to the rôle of these several antigen-antibody systems in the pathogenesis of the poststreptococcal and non-suppurative disorders cannot be profitable. The great importance of these serious pathologic states demands that all of these phenomena be further investigated and the effect of the injection of various antigens in purified form in human beings determined.

SUMMARY

1. A large number of group A hemolytic streptococcal respiratory infections in young men have been studied.

2. No relationship was discovered between any clinical feature of the disease or its complications and the ability of the infecting hemolytic streptococcus to form fibrinolysin *in vitro*.

3. The serum concentration of anti-fibrinolysin was low in 90 per cent of the subjects at the onset of their infection.

4. An increase in antibody of significant magnitude had occurred in 35 per cent of these patients by the fourth week after the onset of acute respiratory illness.

5. An antibody response occurred more frequently when the respiratory disease was severe or when a suppurative or non-suppurative complication supervened.

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Immediate Pressor Effect of Desoxycorticosterone Acetate in Arterial Hypertension*

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REPEATED intramuscular injections of desoxycorticosterone acetate (DCA) and sodium chloride have been reported to produce renal vascular lesions in rats,¹ to elevate the blood pressure of patients with arterial hypertension^{2,3} and to elevate the blood pressure above normal in patients with Addison's disease when they are given in sufficient amounts.⁴ The blood pressure of normal individuals has also been raised by intramuscular injections of DCA but only after more prolonged treatment.⁵ The present report deals with the effect of intravenous injections of DCA and other related hormones upon the blood pressure of both normotensive and hypertensive human subjects.

METHODS

A Hamilton optical manometer was used to record direct arterial pressure before, during and after the injection of test substances.⁶ The ear and finger pulses were recorded in thirty-two instances by photoelectric plethysmography. The electrocardiogram (lead II) was taken after two injections of DCA. The cardiac output was estimated by the ballistocardiograph in seven instances. The venous pressure was measured by an optical manometer in six instances and the skin temperature was followed in three instances by copper-constantan thermocouples. (Figs. 1 and 2.)

The recipients of the various injections were eleven hypertensive subjects, five

normotensive subjects and four exhibiting coarctation of the aorta with normal diastolic pressures. The various substances tested intravenously were DCA, progesterone, Δ^5 pregnenolone, testosterone, dehydroisoandrosterone acetate and 17-hydroxy-11-dehydrocorticosterone. (Fig. 3.) As most of these compounds are quite insoluble in water, 5 mg. of each crystalline steroid compound was dissolved in 2.5 ml. of propylene glycol.^{7,8} Sixteen experiments were controlled by the injection of 2.5 ml. of propylene glycol. In addition 10 ml. of adrenal cortical extract were injected into three hypertensive individuals, controlled by the injection of 10 ml. of 10 per cent alcohol. To facilitate dissolving the crystalline steroids in propylene glycol the solutions were warmed over a steam bath for several minutes. An attempt was made to dissolve desoxycorticosterone, but it was found to be only slightly soluble in propylene glycol and therefore was not used in the present experiments.

In four experiments the response of the blood pressure to a single intramuscular injection of 10 mg. of DCA in peanut oil was followed for several days by the auscultatory method. Similarly, the response to 5 mg. of DCA given intravenously was followed in seven instances. All patients given DCA received 5 to 8 Gm. of sodium chloride in their diets, except one (T. A.) who received 2 Gm. for eight days prior to the experiment.

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RESULTS

A significant, slowly developing rise in blood pressure (16 to 33 mm. Hg diastolic) followed the intravenous injection of DCA in hypertensive subjects. (Table 1.) This rise

sterone acetate, adrenal cortical extract and 17-hydroxy-11-dehydrocorticosterone did not show significant pressor effects when injected into hypertensive subjects. (Table 1.) Since these compounds were inactive on

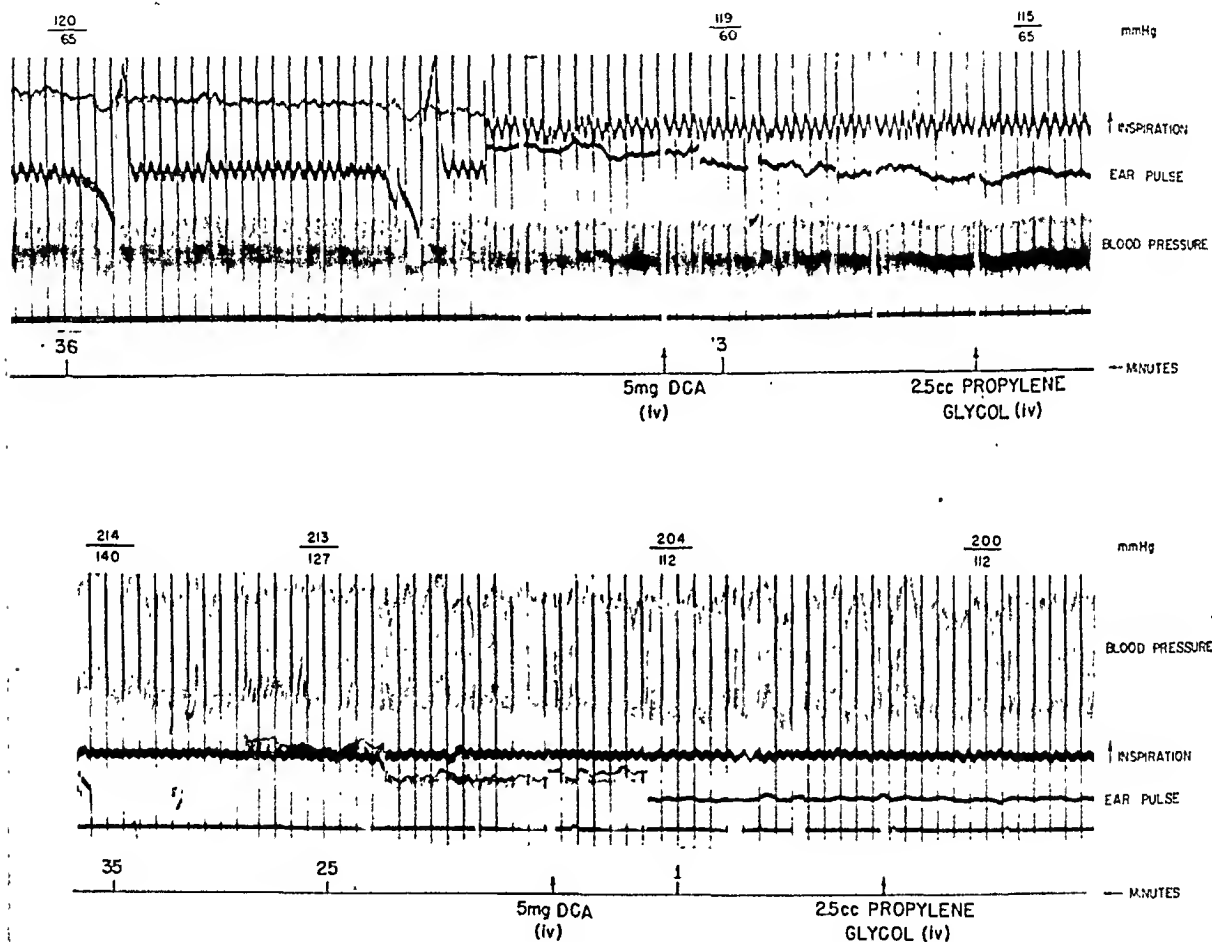


FIG. 1. The effects on blood pressure, ear pulse and respiration of the intravenous injection of propylene glycol and of DCA in propylene glycol in a normotensive (V.E.) (upper graph) and a hypertensive (I.H.) (lower graph). (Record reads from right to left.) Blood pressure values (in mm. Hg) are the average during one minute. Representative sections were taken from the original continuous records. The black vertical lines are at six-second intervals. The interruptions in the blood pressure record indicate duration of injections. The normotensive record shows the effect on blood pressure and ear pulse with voluntary deep inspiration and expiration. In the lower graph DCA was injected five minutes after propylene glycol. Note the gradual rise in diastolic pressure.

became apparent about ten minutes after the injection and lasted from one-half to forty-eight hours. Other steroids used as controls, namely, progesterone, Δ^5 pregnenolone, testosterone, dehydroisoandro-

blood pressure in hypertensives, they were not used in normotensive individuals. In no case did DCA cause a significant elevation of the diastolic pressure of normotensive subjects. These included four patients with

TABLE I
CHANGES IN BLOOD PRESSURE (MM. HG) AFTER AN INTRAVENOUS INJECTION OF 5 MG.
OF DESOXYCORTICOSTERONE ACETATE AND OTHER STEROIDS

Patient	Substance *	Controls				5 mg. DCA			
		Before	After	Maximum Change	Time of Change (min.)	Before	After	Maximum Change	Time of Change (min.)
Hypertensive									
F. W. ♀	P. G.	208/131	213/134	+ 5/+ 3	2	213/134	217/150	+ 4/+16	16
L. C. ♀	P. G.	237/110	232/127	- 5/+17†	35	232/127	280/160	+48/+33	10
I. H. ♀	P. G.	203/115	209/122	+ 6/+ 7	5	209/122	217/145	+ 8/+23	30
	Progesterone	191/105	203/115	+12/+10	10				
D. R. ♀	P. G.	216/120	226/130	+10/+10	6	229/135	240/150	+11/+15	17
	Progesterone	226/130	229/135	+ 3/+ 5	10				
B. C. ♂	P. G.	175/120	169/120	- 6/ 0	19	168/117	180/128	+12/+11	25
	Testosterone	169/120	168/117	+ 1/+ 3	22				
T. A. ♂	197/157	217/175	+20/+18	10
M. L. ♀	217/ 98	235/122	+18/+24	5
D. B. ♀	188/105	215/128	+27/+23	11
M. P. ♀	P. G.	183/101	211/119	+28/+18†	12				
	Δ ⁵ Pregnenolone	211/119	219/127	+ 8/+ 8	13				
	Dehydroisoandrosterone	219/127	214/121	- 5/- 6	25				
D. R. ♀	P. G.	215/128	231/137	+16/+ 9	5				
	Δ ⁵ Pregnenolone	231/137	236/147	+ 5/+10	26				
	Dehydroisoandrosterone	236/147	244/151	+ 8/+ 4	16				
F. W. ♀	Testosterone	194/115	210/125	+16/+10	20				
F. W. ♀	P. G.	185/110	200/118	+15/+ 8	16				
	Compound E	190/110	193/118	+ 3/+ 8	24				
D. B. ♀	Compound E	168/100	198/116	+30/+16	20				
D. B. ♀	Compound E	200/119	203/125	+ 3/+ 6	17				
W. D. ♂	10 ml. ethanol (10%)	214/123	214/127	0/+ 4	5				
	Adrenal cortical extract (10 ml.)	214/127	212/124	- 2/- 3	35				
F. W. ♀	10 ml. ethanol (10%)	194/106	208/113	+14/+ 7	4				
	Adrenal cortical extract (10 ml.)	208/113	199/115	- 9/+ 2	20				
W. D. ♂	Adrenal cortical extract (10 ml.)	201/115	195/117	- 6/+ 2	25				
Normotensive									
W. G. ♂	P. G.	122/ 64	130/ 66	+ 8/+ 2	6	130/ 66	133/ 66	+ 3/ 0	15
V. E. ♀	P. G.	114/ 56	119/ 60	+ 5/+ 4	3	119/ 60	120/ 64	+ 1/+ 4	34
J. M. ♂	P. G.	101/ 63	102/ 62	+ 1/- 1	1	102/ 62	107/ 66	+ 5/+ 4	14
C. C. ♀ †	P. G.	154/ 74	172/ 66	+18/- 8	30	196/ 65	179/ 63	-17/- 2	9
F. R. ♀	P. G.	145/ 61	147/ 65	+ 2/+ 4	34	147/ 65	155/ 70	+ 8/+ 5	14
A. D. ♂	P. G.	200/ 80	212/ 95	+12/+15	4	212/ 95	212/ 93	0/- 2	36
J. F. ♂	171/ 85	168/ 87	- 3/+ 2	42
L. H. ♂	194/ 98	195/108	+ 1/+10	17
L. H. ♀	120/ 60	132/ 61	+12/+ 1	27
E. W. ♂	P. G.	112/ 57	117/ 60	+ 5/+ 3	5	119/ 64	107/ 62	-12/- 2	34
	Progesterone	117/ 60	119/ 64	+ 2/+ 4	24				
M. P. ♀	P. G.	111/ 57	122/ 66	+11/+ 9	4	117/ 64	125/ 68	+ 8/+ 4	12
	Progesterone	122/ 66	117/ 64	- 5/- 2	23	117/ 64	120/ 61	+ 3/- 3	49

* P. G. = 2.5 ml. propylene glycol; 5 mg. progesterone, testosterone, Δ⁵ pregnenolone, 17-hydroxy-11-dehydrocorticosterone (compound E), and dehydroisoandrosterone acetate dissolved in 2.5 ml. propylene glycol.

† Severe pain during injection.

‡ This patient exhibited a high systolic pressure of undetermined etiology.

§ Coarctation of aorta.

Blood pressures indicate the average systolic and diastolic values during one-half to one minute at the period of maximum change.

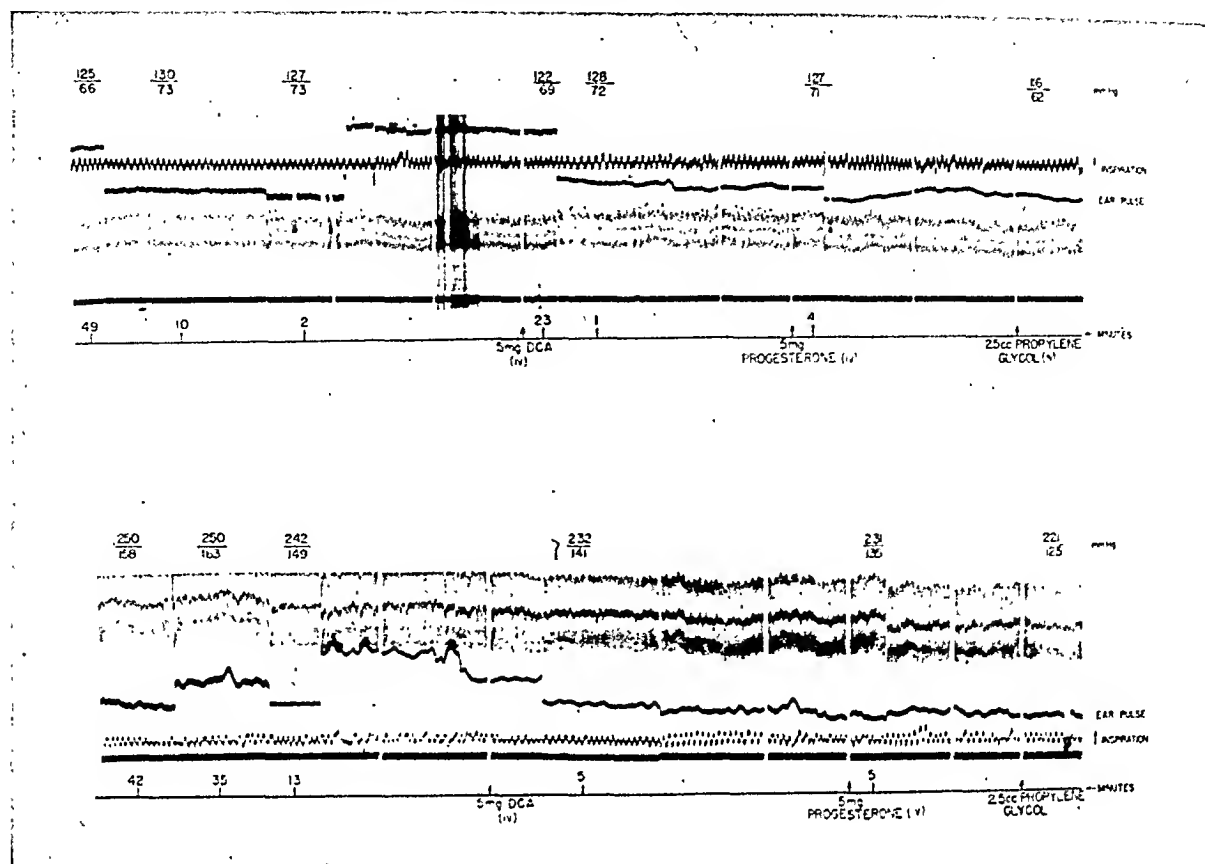


FIG. 2. The effects on blood pressure, ear pulse and respiration of the intravenous injection of propylene glycol, progesterone and DCA in a normotensive (M.P.) (upper graph) and a hypertensive (D.R.) (lower graph). (Notations same as Figure 1.) The black vertical line on the upper record indicates the end of the injection of DCA. The systolic pressures at thirteen, thirty-five and forty-two minutes of the lower record were obtained by calibration of the kymographic camera scale since the photographic paper was not wide enough to record these values. Note the very slight effect of progesterone as compared to DCA.

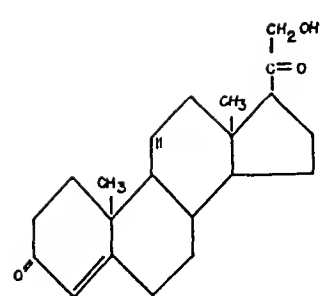
TABLE II

PROLONGED BLOOD PRESSURE RESPONSE TO INTRAMUSCULAR AND INTRAVENOUS INJECTIONS OF DCA IN HYPERTENSIVE PATIENTS (MM. HG)

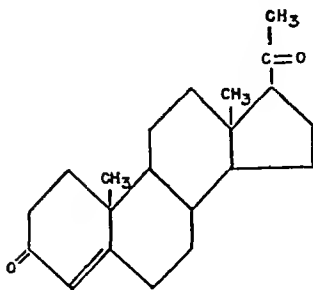
	10 mg. DCA Intramuscularly				5 mg. DCA Intravenously			
	Average Blood Pressure Before	Average Blood Pressure After	Change	Days* After DCA	Average Blood Pressure Before	Average Blood Pressure After	Change	Days* After DCA
L. C. ♀	178/108	208/138	+30/+30	3	204/125	208/134	+4/+9	3
	193/118	204/126	+11/+8	3				
M. L. ♀	153/95	182/104	+29/+9	2	144/84	167/94	+23/+10	5
	150/90	175/117	+25/+27	6				
B. C. ♂	160/93	188/129	+28/+36	2
T. A. ♂	208/160	201/158	-7/-2	1
I. H. ♀	162/98	144/93	-18/-5	4†
D. R. ♀	209/143	212/153	+3/+10	2
D. B. ♀	154/109	172/116	+18/+7	2

* Blood pressure averages were taken for this period of time following the injection of DCA.

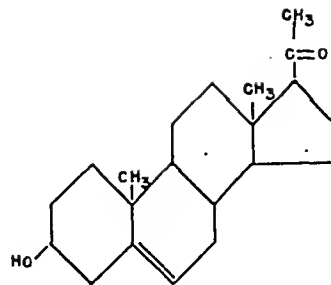
† Experiment done eleven days after 10 mg. DCA intramuscularly for seventeen days.



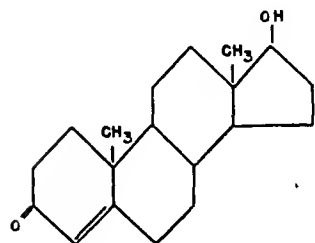
DESOXYCORTICOSTERONE



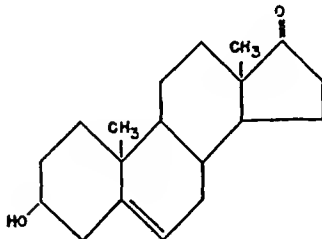
PROGESTERONE



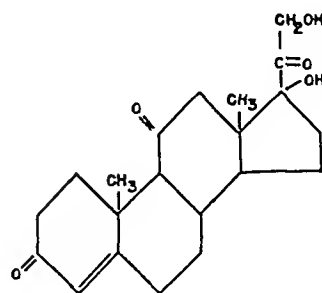
Δ_5 PREGNENOLONE



TESTOSTERONE



DEHYDROISOANDROSTERONE



17 HYDROXY Δ^5 DEHYDRO-CORTICOSTERONE

FIG. 3. The similarity of the chemical structures of the steroids used in these experiments.

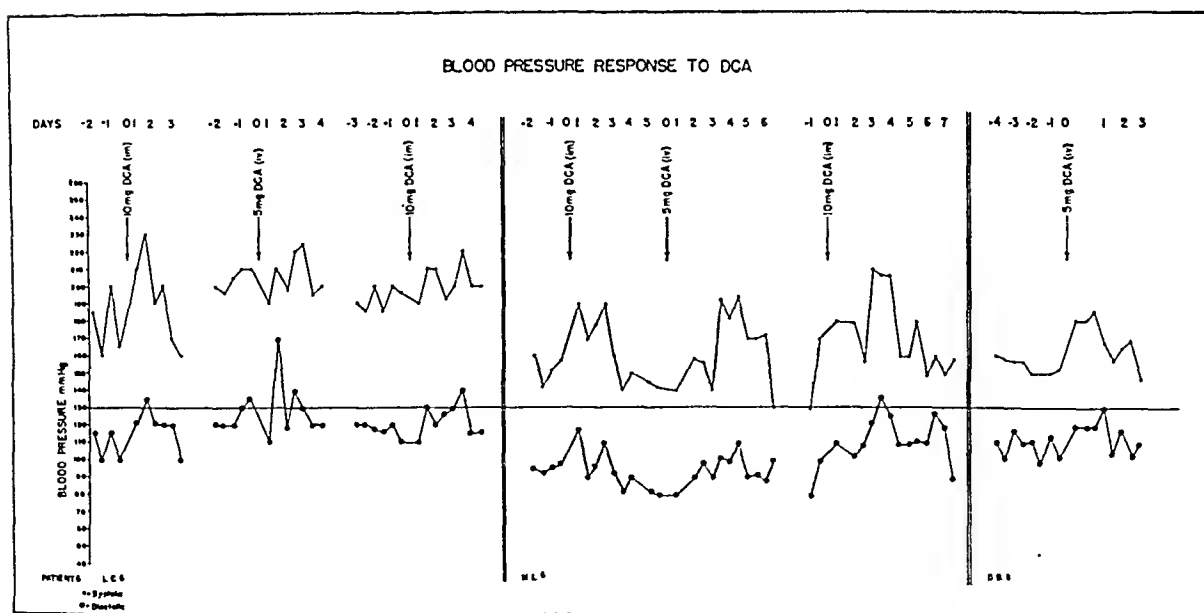


FIG. 4. Prolonged response of blood pressure in three hypertensive subjects following a single intravenous or intramuscular injection of DCA. Blood pressures were recorded twice daily (8:00 A.M. and 2:00 P.M.) after thirty minutes of bed rest by the auscultatory method. The upper level represents the systolic, the lower represents the diastolic pressure.

coarctation of the aorta who exhibited normal diastolic pressures in both brachial and femoral arteries as measured with a Hamilton manometer.

Sometimes the injection of propylene glycol caused pain along the course of the vein. This was immediately abolished by subsequent injection of normal saline solution. This pain was inconstant but when present appeared to affect blood pressure in two hypertensive individuals. There was no correlation between the presence of pain (which was momentarily severe during ten injections and slight during 12) and the eventual action of the compound injected.

Three of seven hypertensive patients responded to a single injection of 5 mg. of DCA intravenously or 10 mg. intramuscularly by a significant rise in both systolic and diastolic pressures for as long as forty-eight hours. (Table II, Fig. 4.) In addition, these patients complained of exacerbation or intensification of their clinical symptoms such as headache, nervousness and restlessness.

COMMENTS

From the results of these experiments a question arises as to the manner in which DCA affects the blood pressure. Judging from the ballistocardiographic studies, the cardiac output was not increased. Perera et al. have shown, when DCA is injected intramuscularly over several days, that the increase in blood pressure in hypertensive individuals cannot be correlated with abnormal retention of the sodium ion or with an increase in circulating blood volume.³ The circulation in the ear lobe, fingers and toes did not decrease as would occur if there had been vasoconstriction in these areas. It is possible, therefore, that visceral vascular beds may have been affected.

The four subjects exhibiting coarctation of the aorta deserve comment. All of them showed normal diastolic pressures although their systolic levels were relatively high. Their failure to respond to the intravenous injection of DCA suggests that their systolic hypertension was not on the same basis as

patients with diastolic hypertension. It will be necessary to compare these patients with others having coarctation and elevated diastolic pressures.

Three of seven patients appeared to be extremely sensitive to administration of DCA, responding by prolonged increases in the levels of blood pressure and by exacerbation of their symptoms. Whether these increases exhibit a different type of the disease in which the activity of the adrenals is relatively greater, as distinguished from the usual case of arterial hypertension, remains to be elucidated. At any rate, it would seem that DCA, a compound chemically related to adrenal cortical hormones, acts as a pressor substance when hypertension is already established.

SUMMARY

1. Five mg. of DCA,* progesterone, Δ^5 pregnenolone, testosterone, dehydroisandrosterone acetate, 17-hydroxy-11-dehydrocorticosterone† (dissolved in 2.5 cc. of propylene glycol) and 10 ml. of adrenal cortical extract were injected intravenously into twenty patients, of whom eleven exhibited elevated diastolic pressures and nine did not.

2. Of these substances only DCA acted as a pressor substance and then only in hypertensive subjects. Its pressor effect was prolonged.

Acknowledgments: We are indebted to Drs. Willard M. Allen and Joseph C. Jaudon for donating some of the compounds used. The advice of Dr. Konrad Dobriner and the technical assistance of Sallie Wood, R.N., Julia Finn and Mary Kinsella is gratefully acknowledged.

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* Supplied by Schering Corporation.

† Supplied by Parke, Davis & Company.

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Prolongation of the Coagulation of Whole Blood by Dicumarol in Man*

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USE of dicumarol for the prevention of intravascular clotting has become increasingly widespread in clinical practice.¹ While it is well established that dicumarol in adequate amounts causes prolongation of the blood prothrombin time, it has little influence on the clotting time of whole blood as carried out in glass tubes until the prothrombin clotting time has been greatly prolonged.² Thus it has been difficult to explain the prevention of intravascular clotting by dicumarol in amounts which fail to alter significantly the whole blood clotting time and cause only a moderate decrease in the prothrombin clotting time, particularly since Quick³ has shown that much lower prothrombin levels are necessary to inhibit clotting *in vitro*.

However, an increasing number of reports have indicated the effectiveness of comparatively small doses of dicumarol in preventing thrombosis.^{4,5} Such clinical observations raise the question of whether or not dicumarol influences the coagulation of blood in a manner which is not accurately reflected by the prothrombin clotting time or by the clotting time of whole blood in glass tubes. In the investigation herein reported this problem has been studied employing glassware coated with a silicone (drifilm)|| following the method described by Jaques and co-workers.⁶

|| This material was supplied by the Research Division of the General Electric Co. (General Electric Drifilm No. 9987.)

* From the Clinical Research Laboratory, Holy Ghost Hospital, Cambridge, Mass. This study was supported by a grant from the American Cancer Society and is part of an investigation on blood coagulation in malignant diseases.

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METHODS AND MATERIALS

Studies were carried out in a group of eleven male and female patients, of whom seven had multiple sclerosis, one had Friedreich's ataxia and three had generalized arteriosclerosis. In most cases dicumarol was given orally in dosage of 300 mg. the first day, 200 mg. the second day and thereafter usually reduced to 100 mg. a day.

Prothrombin clotting times were carefully performed using Quick's method³ and employing 0.020 M calcium chloride solution. Rabbit brain thromboplastin was used and a dilution curve for control plasma was plotted. The prothrombin clotting time was reported in per cent of normal.

Whole blood clotting time was determined by a modification of the method of Lee and White.⁷ Blood was obtained with a swift, clean venipuncture using a sharp No. 19 needle; very little tourniquet pressure was used and the patient was bled without use of a syringe. Discarding the first portion, the free-streaming blood was allowed to flow down the inside of a 100 by 16 mm. plain glass tube, avoiding bubbles and agitation. The tubes were immediately placed in the water bath at 37°C.

The clotting time in glass, as measured by an end point of definite jelling of the blood, was from five to twelve minutes in normal controls and in patients before dicumarol therapy. Occasionally, using this technique, a clotting time up to fifteen minutes was observed in healthy controls; for the purposes of this paper an arbitrary limit of clotting time of over fifteen minutes in glass at 37°C. was considered abnormal.

Bleeding into drifilmed tubes was carried out exactly as done for the glass tubes. The glass tubes were carefully coated with drifilm but variable results were obtained if the tubes were redrifilmed after use; in this study tubes were drifilmed and used only once. The quality of

prolonged. Since contamination with tissue juice causes remarkably decreased clotting time in drifilm and invalidates the clotting tests,⁶ with a poor or difficult venipuncture the test was discarded and a fresh venipuncture was carried out.

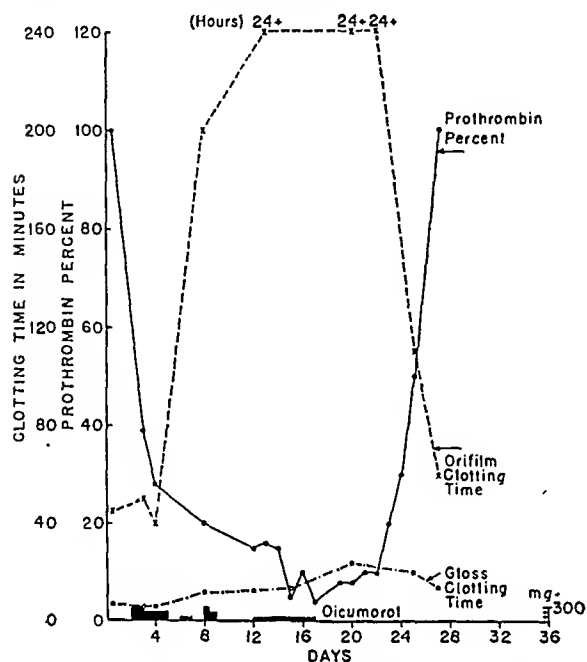


FIG. 1. F. C., fifty-three, a white male with multiple sclerosis. Graph illustrating the marked prolongation of the clotting time in drifilm tubes compared to the clotting time in glass tubes following the administration of dicumarol.

the water caused a marked difference in the drifilm surface. On one occasion when tap water instead of distilled water was used in preparation of the tubes, the procedure was completely spoiled. It was found that results were just as accurate without drifilming the needles and better tests were obtained when the use of drifilmed syringes was discontinued.

The temperature at which the drifilm clotting times were carried out greatly influenced the clotting time. Jaques and his associates⁶ found that at ice box temperature blood remained unclotted for many hours in drifilm and this finding was repeatedly confirmed in our experience. At room temperature clotting times were longer but more variable than at body temperature. Hence in this work the clotting studies were carried out in a water bath at 37°C. In normal controls the clotting time of whole blood in drifilm varied from thirty to sixty minutes and a clotting time of over sixty minutes at 37°C. was considered abnormally

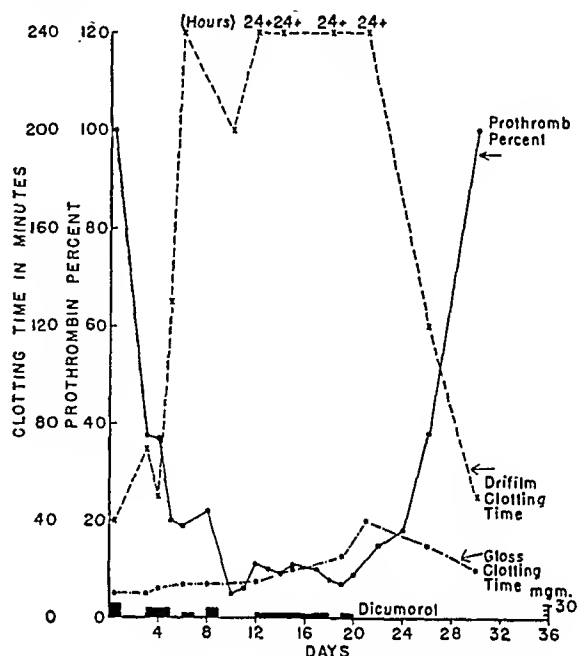


FIG. 2. C. M., seventy-five, a white male with generalized arteriosclerosis. Demonstrating the effect of dicumarol on the clotting time of whole blood in drifilm tubes as compared to glass tubes.

RESULTS

As indicated in Figures 1 to 4, following administration of dicumarol, an increase in the prothrombin clotting time usually occurred within forty-eight hours but the degree of hypoprothrombinemia varied considerably. The clotting time in drifilm became definitely prolonged after forty-eight hours and when 700 mg. to 900 mg. of dicumarol were given over a seven-day period, prolongation of the drifilm clotting time for periods of from twenty-four to seventy-two hours or longer was observed. At the same time the clotting of whole blood in glass was prolonged slightly or not at all until very marked depletion of prothrombin occurred.

COMMENTS

Clotting of blood as observed in glass represents an artificial and false reflection

of the true state of intravascular blood coagulability. In the past, paraffin, collodion and plastics such as lusteroid have been employed to simulate more closely the endothelial surface.^{8,9} Davidson and MacDonald² observed that in patients given

clotting time in glass, dicumarolized blood in drifilm tubes took twenty-four hours or longer to clot. These observations provide laboratory support, hitherto lacking, for the accumulating clinical evidence that dicumarol may be effective in prevention

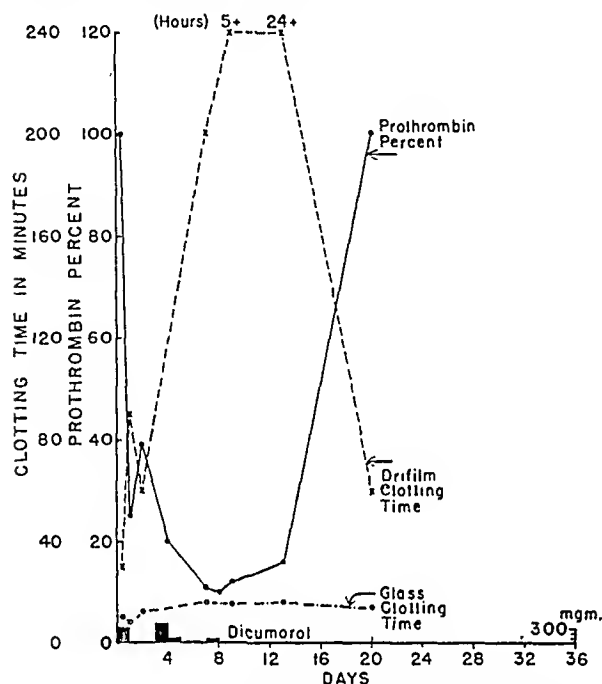


FIG. 3. P. M., sixty-five, a white male with generalized arteriosclerosis and arteriosclerotic heart disease. Graph illustrating the prolongation of clotting time in drifilm tubes compared to normal clotting time in glass tubes.

massive doses of dicumarol, the clotting time of whole blood in lusteroid was much more prolonged in relationship to the fall in prothrombin clotting time than was the clotting time in glass. Although there was a marked variability of the clotting time in lusteroid, these authors concluded that the coagulation time in lusteroid indicated the true coagulation defect more closely than did glass.

The recent work of Jaques and his co-workers⁶ on the effect of a silicone in prolonging the clotting time offers a new method for the study of blood coagulation. With certain modifications, as just noted, the silicone technic was employed in this study of the effect of dicumarol on the clotting mechanism. As a result it was demonstrated that at prothrombin levels which were not low enough to influence the

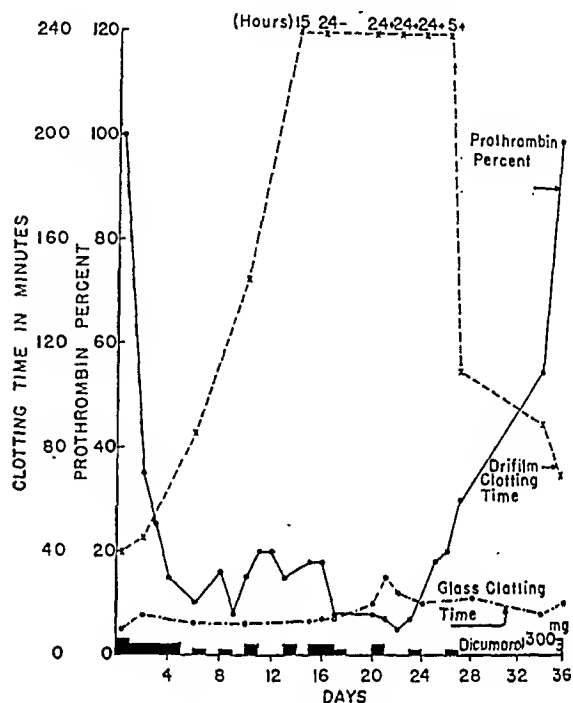


FIG. 4. R. K., fifty-five, a white male with multiple prolongation of the clotting time of whole blood in drifilm tubes and the delayed moderate elevation of the clotting time in glass tubes following the administration of relatively large amounts of dicumarol.

of intravascular clotting even in dosages which are inadequate to produce critically low prothrombin activity or prolongation of the clotting time in glass.

From the clinical standpoint the estimation of clotting time as carried out in glass tubes is of little practical value in the management of the dicumarolized patient. Clotting tests in drifilm require rather exact technic and for routine use would not be a practical method at present. However, development of a plastic necessitating less care in preparation of the tubes and providing a more permanent surface will undoubtedly extend the usefulness of this type of material in the study of blood coagulation. In our present state of knowledge the careful determination of the prothrombin

clotting time is the best laboratory method of controlling the clinical use of dicumarol.

SUMMARY

1. Dicumarol administered to a series of eleven patients caused a greatly prolonged clotting time of whole blood in drifilmed tubes. The clotting time in glass tubes did not accurately reflect this coagulation defect.

2. The data presented support the clinical impression that intravascular clotting may be prevented, at least in part, by amounts of dicumarol which fail to depress the prothrombin activity of the blood to levels hitherto considered necessary for the inhibition of clotting.

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Thephorin in Allergy*

A Study of 292 Cases

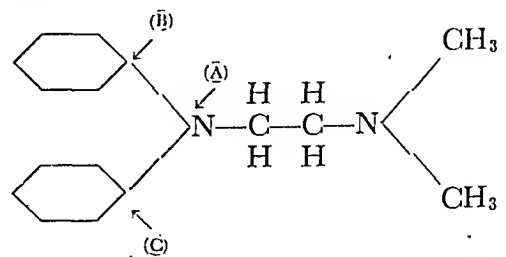
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THE history of the development of antihistaminic compounds has been reviewed by Feinberg.¹ A description of anaphylaxis and of the parallelism between its symptoms and those of certain allergic states was accomplished over fifty years ago, and eventually led to the application of specific desensitization procedures in clinical allergy. Research has more recently turned to the discovery of a method which would inhibit the anaphylactic or allergic process without recourse to the use of specific antigens. In 1932 Hill and Martin² reported that until that date 165 substances or techniques had been investigated for such non-specific inhibition. Among them were bizarre therapeutic agents, including benzene in large doses, low atmospheric pressures and extracts and cultures of *Mycobacterium tuberculosis*. Also tried were atropine, ether, chloral hydrate, barium and many non-specific sera and proteins. In 1944 Feinberg³ listed many other methods; among them were the barbituric acid derivatives, salts of sodium and potassium, vitamin C, vitamin P (hesperidin) and ethylene disulfonate, all tried and found wanting.

Workers in allergy are generally agreed that chemical agents common to all anaphylactic and allergic reactions must be responsible for the clinical signs and symptoms; the picture produced falls into one of a few predictable patterns no matter which of a great variety of antigens is applied to the sensitized organism. A long series of investigations has led to the conclusion that histamine is one such chemical agent and may be, in part, responsible for the clinical manifestations observed in allergic individuals.

Direct attacks on the histamine factor in the allergic reaction have followed a logical pattern. First, desensitization by injection of small amounts of histamine itself was tried. Review of clinical and laboratory investigations into this technique suggests that its usefulness, if any, is limited.⁴⁻⁷ Since injection of histamine failed to produce antihistaminic substances, it was hoped that a protein-histamine conjugate might stimulate the formation of antibodies. A variety of proteins, ranging from casein to dog serum, has been linked to histamine; however, the investigations reported to date fail to prove that the use of these conjugates materially increases immunity or histamine tolerance.⁸⁻¹¹ Finally, a histamine-destroying enzyme, histaminase, was tried. Feinberg¹ reviewed thirty contributions to the literature on histaminase and suggested that its efficacy *in vitro* had not been duplicated *in vivo*.

Several chemical agents which seem to compete with histamine in biochemical reactions have shown promise in the symptomatic relief of the allergies. Four of the most effective compounds, two French (antergan and neoantergan) and two American (benadryl and pyribenzamine) have the same basic structural formula:



In benadryl an ether linkage is substituted for the nitrogen atom at (A). Pyribenzamine

* From the Allergy Service, Department of Medicine, Wisconsin General Hospital, Madison, Wis.

has a carbon atom added at (B) and a nitrogen atom substituted for the carbon at (C). Thephorin,* the drug employed in the present investigation, is a polycyclic amine, the empiric formula of which is $C_{19}H_{19}N$. The laboratory investigations of the antihistaminic action of thephorin which have been recorded¹² and two preliminary reports of the clinical efficacy of the drug^{13,14} suggest that it merits careful clinical evaluation.

Reports of clinical investigations of antihistaminic agents are difficult to evaluate and almost impossible to compare. Some workers have been content to report a percentage of patients "improved" or "unimproved" without trying to quantitate the change. Allergic manifestations are prone to cyclic changes. The phenomena under consideration lend themselves poorly to objective analysis. In November, 1946, in a report to the Council on Pharmacy and Chemistry of the American Medical Association,¹ the following criteria were suggested to test the effectiveness of a symptomatic remedy in allergic disease:

"1. Unquestioned relief of symptoms must be obtained on the administration of the drug on repeated occasions.

"2. Recurrence of symptoms should follow the discontinuance of the medicament.

"3. The relief should be obtained under conditions sufficiently controlled and under varying circumstances so that it cannot be attributed to normal fluctuations in tolerance or to external factors such as weather or pollen concentration.

"4. Wherever possible, objective changes should confirm subjective claims.

"5. Placebo medication should fail to produce relief."

The present study falls short of the mark in several of these categories.

In this investigation, 292 allergic patients were followed during the year 1947. The effect of medication was charted on weekly visits to the allergy clinic. Quantitation of

* Brand of Phenindamine (2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate) supplied by Hoffmann-La Roche, Inc., Nutley, N. J. Thephorin Trade Mark Reg. U.S. Patent Office.

subjective response was attained by training patients to think in terms of severity and frequency of attacks. If asthmatic seizures were less than one-half as severe immediately after medication was begun, 50 per cent relief was recorded; if less than one-half

TABLE I

SIDE REACTIONS TO THEPHORIN IN 54 OF 292 PATIENTS

Gastrointestinal.....	19
*Nausea and vomiting.....	(4 patients)
*Constipation.....	(3 patients)
Abdominal pain	
Thirst	
Anorexia	
Nervous.....	33
*Stimulation.....	(2 patients)
*Weakness.....	(2 patients)
Insomnia	
Palpitation	
Drowsiness	
Headache	
Urticaria.....	1
Urinary urgency and frequency.....	1

* These eleven patients discontinued medication for the reasons indicated by asterisk. All other reactions were readily controlled, or sufficiently mild to permit uninterrupted treatment with thephorin.

as frequent, 50 per cent relief was recorded; if both, 75 per cent relief was recorded. Although placebos were not used, 142 patients were treated with thephorin and other antihistamine drugs alternately and they were asked to compare results.

Eighty-three cases of asthma were observed; of these, fifty-eight were studied in some detail. The majority were extrinsic (forty-four), the minority intrinsic or bacterial (fourteen). Ages ranged from two to seventy-one; the weight distribution followed a normal curve. There were thirty-one males and twenty-seven females. The duration of the disease was over twelve years in 60 per cent of the cases. Thirty had previously used benadryl, eighteen with unpleasant side reactions. Twenty-four had previously used pyribenzamine, seven with unpleasant side reactions. Of the eighty-three asthmatics on thephorin, eighteen had reactions, four of these requiring discontinuance. (Table 1.) Comparison of the efficacy of thephorin with that of other drugs used was most interesting. Of twenty-one asthmatic patients alternating with pyribenzamine, sixteen thought thephorin

more effective, three thought them equally effective and two preferred pyribenzamine. Of twenty-four alternating with benadryl, seventeen thought thephorin better, six reported the two drugs to be equally effective and one preferred benadryl. It must be borne in mind in making such comparisons that this series is heavily weighted in favor of thephorin, in that many patients volunteered for the experiment because they were dissatisfied with their response to one of the other antihistaminic drugs. Percentage of relief for the asthmatic patients was recorded as follows: 0 to 49 per cent relief, twenty-six; 50 to 74 per cent relief, fifteen; 75 to 100 per cent relief, forty-two patients. (Table II.) The adequate daily dose ranged from 50 to 200 mg.

One hundred sixty-one patients with allergic rhinitis were treated with thephorin. Of these, 131 were studied in some detail. Ages ranged from two to seventy. There were seventy-four males and fifty-seven females. Duration was over twelve years in 42 per cent of the cases. Sixty-two had previously used benadryl, thirty-eight with unpleasant reactions. Forty-six had previously used pyribenzamine, eleven with unpleasant reactions. Of the 131 patients with allergic rhinitis, twenty-seven complained of side effects, but only five discontinued thephorin medication. (Table I.) Again, direct comparison with other drugs was weighted heavily in favor of thephorin. Of forty-two patients alternating with pyribenzamine, twenty-eight thought thephorin more effective, five thought them equally effective and nine preferred pyribenzamine. Of fifty-three alternating with benadryl, thirty-eight thought thephorin better, eight reported the drugs to be equally effective and seven preferred benadryl. Percentage of relief for the allergic rhinitis patients was recorded as follows: 0 to 49 per cent relief, thirty-three; 50 to 74 per cent relief, twenty-three; 75 to 100 per cent relief, 105 patients. (Table II.) The adequate daily dose ranged from 25 to 200 mg.

Other allergic conditions, such as mi-

graine, angioneurotic edema and allergic dermatitis were treated in numbers too small to be statistically significant. These thirty-eight cases are therefore summarized without comment in the accompanying table.

TABLE II
THEPHORIN IN 292 CASES OF ALLERGY

Diagnosis	Cases	Good Result (75-100% Relief)	Fair Result (50-74% Relief)	Poor Result (0-49% Relief)
Asthma.....	83	42	15	26
Allergic rhinitis.....	161	105	23	33
Angioneurotic edema....	18	13	0	5
Allergic dermatitis.....	18	5	4	9
Migraine.....	12	8	0	4

SUMMARY

1. A new antihistaminic drug, chemically unrelated to others now available, was employed in the management of 292 allergic patients.

2. The symptomatic relief observed and the paucity of untoward reactions reported suggest that this drug deserves extensive clinical trial.

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Agranulocytosis during Propylthiouracil Therapy*

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BEFORE a conclusion is justified as to the incidence of reactions of any new drug treatment of many patients is necessary. In our use of thiouracil it was determined after treating 400 patients that reactions occurred in 9 per cent of the subjects. Since no difficulty was encountered during treatment of the first forty-five patients, the conclusion could have been reached that thiouracil could be administered without danger. Among the next ten patients treated, agranulocytosis occurred in three cases which forcibly indicated that there was real danger in administering thiouracil.

The initial report on the use of propylthiouracil in hyperthyroidism by Astwood and Vander Laan dealt with the treatment of one hundred patients. As they observed no significant side effects they gained the impression that propylthiouracil was a completely safe drug. Baird, in a critique on thyroidectomy in hyperthyroidism, used the absence of reactions to propylthiouracil as strong evidence in favor of drug therapy. He reported that in several thousand patients treated with propylthiouracil only a few minor reactions occurred and in no patient was it necessary to discontinue the drug. Reveno observed fifty-four hyperthyroid patients treated with propylthiouracil. In no instance was there an alteration in the leukocytes. Fever developed in one patient after forty-one days of therapy; a test dose one week after withdrawal of propylthiouracil caused recurrence of fever in four hours, showing definite sensitivity.

A serious reaction following propylthiouracil therapy was reported by Livingston

and Livingston. Agranulocytosis and hepatocellular jaundice developed in this patient after six weeks of treatment with propylthiouracil in a daily dosage of 150 to 200 mg. The peripheral blood and bone marrow revealed an absence of granulocytes; the leukocyte count was 1,050. Recovery followed intensive therapy with penicillin and streptomycin. A case in which moderate leukopenia (2,100 cells) and granulocytopenia (22 per cent) developed was reported by Eisenmenger and Steele. Changes in the blood took place after four months of propylthiouracil in a daily dose of 150 to 200 mg. Previously moderate leukopenia (3,400 cells) and granulocytopenia (40 per cent) had developed in this patient after six months of therapy with thiouracil.

There were seven toxic reactions among 218 hyperthyroid patients treated by McCullagh and his associates. These reactions consisted of nausea, arthralgia and numbness of the extremities which were not severe enough to require stoppage of therapy. In four patients, treatment was discontinued because of the development in each case of either severe exfoliative dermatitis, numbness of the extremities, granulocytopenia of 25 per cent or urticaria. Since they had not observed agranulocytosis, they discontinued weekly blood counts and advised blood studies only in the event of sore throat. McGavack encountered but one reaction to propylthiouracil in seventy-five patients. This consisted of fever and generalized rash after nine days on a dose of 50 mg. of propylthiouracil daily. A similar reaction occurred after five days of treatment with thiouracil. Williams treated thirty-nine thy-

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rotoxic patients with propylthiouracil and in no patient did a reaction develop. Two of the patients treated had previously shown a reaction to thiouracil (a rash in one case and leukopenia and rash in the other).

TABLE I
REVIEW OF REPORTS FROM THE LITERATURE

Authors	No. Patients Treated	Reactions		
		Type	No.	Per Cent
Astwood-Vander Laan.....	100	Urticaria	2	2.0
Reveno.....	54	Fever	1	1.8
McCullagh-Hibbs-Schneider	218	Nausea	1	
		Arthralgia	1	
		Numbness of extremities	2	
		Severe dermatitis	1	
		Granulocytopenia	1	
		Urticaria	1	
			7	3.2
McGavack et al.....	75	*Generalized rash with fever	1	1.3
Williams.....	39	0		
Total.....	486		11	2.0
Livingston and Livingston..	?	Agranulocytosis and hepatitis	1	
Eisenmenger-Steele.....	?	*Leukopenia with granulocytopenia	1	
Shibley.....	?	Agranulocytosis	1	

* Similar reaction to thiouracil.

A review of eight reports (Table I) dealing with the use of propylthiouracil reveals agranulocytosis to have occurred twice. Granulocytopenia sufficient to warrant withdrawal of treatment occurred in two patients, generalized rash in two patients, urticaria in three and fever in one. Numbness of the extremities, nausea or arthralgia were also noted. Among 486 patients treated with propylthiouracil there were eleven reactions, an incidence of 2 per cent.

In the last four and one-half years we have used antithyroid drugs in preoperative preparation for thyroidectomy of 1,100 patients with hyperthyroidism. Four hundred of these patients received thiouracil, with a reaction incidence of 9 per cent (fever, skin eruption, depression of leukocytes, swollen salivary glands and edema of the skin). Twenty-eight patients were given thiobarbital, a very potent antithyroid agent, with a high reaction incidence of 28 per cent (depression of leukocytes and

fever). The remaining 672 patients received propylthiouracil (probacil).* In this latter group there were thirteen definite reactions (Table II), an incidence of 1.9 per cent. Most of the reactions involved the blood,

TABLE II
REACTIONS TO PROPYLTHIOURACIL

A. White blood cell depression	
1. Agranulocytosis.....	3
2. Leukopenia, granulocytopenia or both..	7
B. Fever.....	1
C. Skin irritation.....	1
D. Scleredema.....	1
Total reactions.....	13
Percentage.....	1.6

three patients developed agranulocytosis and seven patients either significant leukopenia, granulocytopenia, or both. Single cases of fever, skin irritations and scleredema were also observed.

The purpose of this paper is to report the observation that changes in the leukocytes occurred in 10 of 672 patients during therapy with propylthiouracil and that agranulocytosis, a serious clinical condition, occurred in three of these. The case reports of the three patients developing agranulocytosis are of chief interest, especially two of which revealed similar blood changes on shifting to thiouracil.

CASE REPORTS

CASE I. A woman, fifty years of age, was initially seen in April, 1946, with signs and symptoms of recurrent hyperthyroidism. She had a thyroidectomy in 1929. She had lost 20 pounds in the previous year and had become extremely nervous. The thyroid remnants were moderate in size, the basal metabolic rate was +24 and the pulse rate 108.

Treatment with propylthiouracil was begun in a daily dose of 75 mg. After thirty days the dose was increased to 150 mg. daily. Blood counts were taken periodically (Fig. 1); the percentage of polymorphonuclear cells remained satisfactory but the total white counts during the fifth and sixth week were around 4,000 cells. Treatment was continued and on the sixtieth day sore throat and fever developed. Total leukocyte count at this time was 1,950, with

* Supplied by Dr. Stanton Hardy of Lederle Laboratories, Pearl River, N. Y.

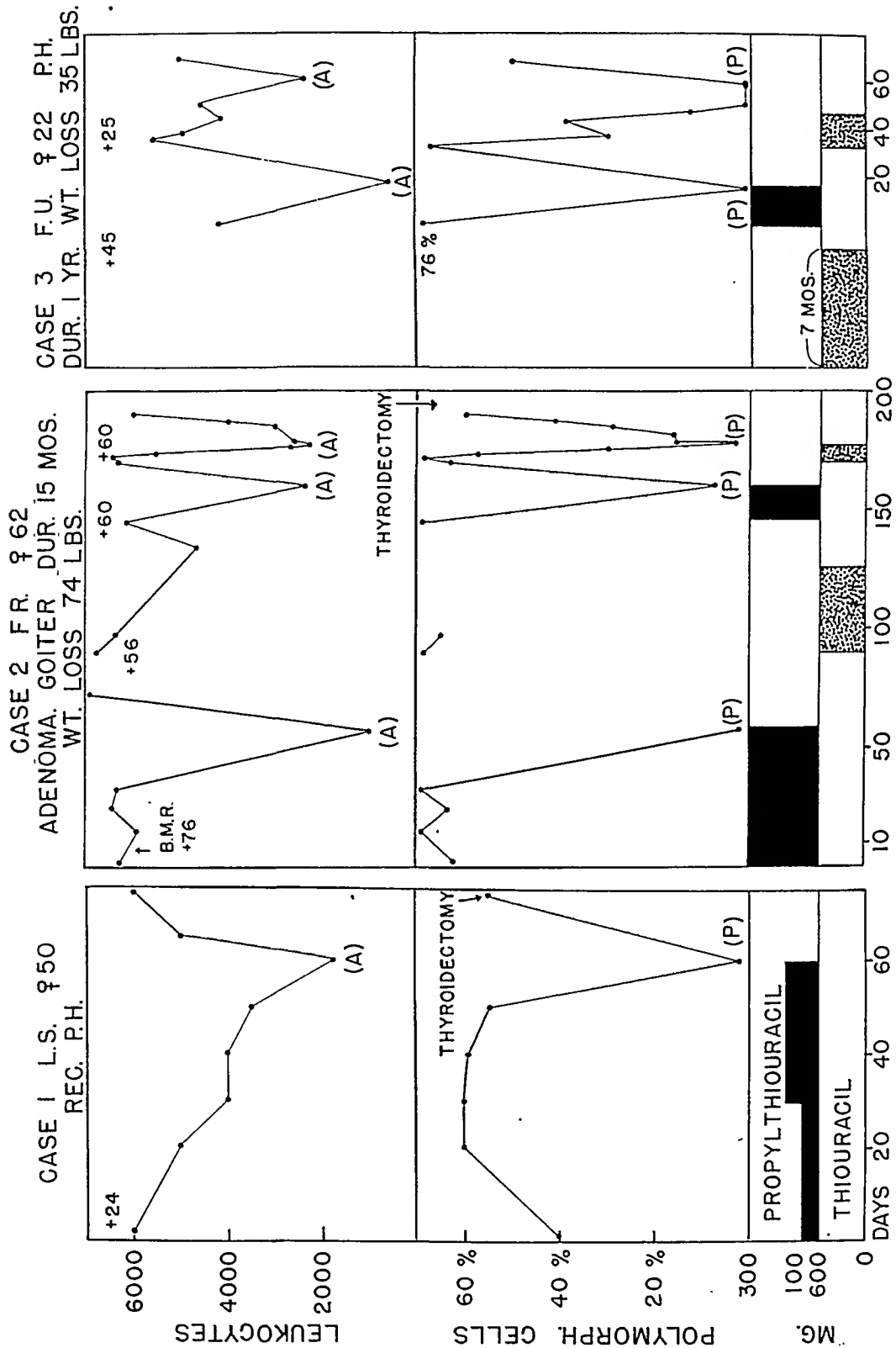


Fig. 1. Three cases of agranulocytosis following administration of propylthiouracil. Case 1 developed agranulocytosis three times, twice following propylthiouracil and once following thiouracil. In Case 2 agranulocytosis followed administration of propylthiouracil and again after thiouracil which had previously been taken for seven months.

1 per cent polymorphonuclear cells. The patient was hospitalized and given penicillin. In eight days the white blood cells returned to normal and a week later the thyroid remnants were surgically removed. The postoperative course was satisfactory.

CASE II. (Fig. 1) A woman, sixty-two years of age, was first seen in May, 1947. She had noted a lump in her neck for seven years. For fifteen months she had symptoms characteristic of hyperthyroidism and had lost 79 pounds in weight. The basal metabolic rate was +76 and the pulse rate 116 beats per minute. In addition to hyperthyroidism she had long-standing hypertension, enlargement of the heart by roentgenologic examination and the electrocardiogram showed left axis deviation.

Treatment was begun with a daily dose of 300 mg. of propylthiouracil. Progress was satisfactory, with normal periodic blood counts until the fifty-fourth day of treatment when a severe sore throat developed. Blood studies showed a leukocyte count of 1,000 with a total absence of polymorphonuclear cells. She was critically ill but recovered following penicillin therapy. In two weeks the white blood cells were normal. Three weeks later, since the patient was still markedly hyperthyroid (basal metabolic rate +56), treatment was begun with thiouracil, 600 mg. daily. She took this for thirty-six days. Treatment then was discontinued for two weeks; blood tests at this time were normal. Thiouracil was again prescribed but through a druggist's error propylthiouracil was given. Sixteen days later she was readmitted to the hospital with agranulocytosis, the white count being 2,000 cells with an absence of polymorphonuclear cells. Penicillin was administered and in fifteen days the white blood cells had returned to normal. Since the patient was still hyperthyroid, basal metabolic rate +60, it was decided to continue antithyroid treatment with thiouracil to which she had not shown any intolerance. After the administration of thiouracil, 600 mg. daily for seven days, the blood was again depressed, the white count being 2,400 and polymorphonuclear cells 4 per cent. Treatment was again instituted with penicillin and in two weeks the blood had returned to normal.

As the patient had twice shown intolerance to propylthiouracil and once to thiouracil it was thought unwise to attempt further antithyroid treatment with other available antithyroid drugs, such as methylthiouracil or thiobarbital,

for fear that agranulocytosis might recur and that the bone marrow might fail to restore itself; thyroidectomy was therefore undertaken on November 28, 1947. The postoperative course was satisfactory but not as smooth as observed in patients under antithyroid control. She was discharged from the hospital on the eighth postoperative day.

CASE III. A woman, twenty-two years of age, was seen on September 22, 1947, with symptoms and signs of severe primary hyperthyroidism. (Fig. 1.) Her symptoms were of eighteen months' duration during which time she had lost 35 pounds. Diagnosis of hyperthyroidism had been made nine months before and she had taken thiouracil irregularly for seven months without control of the disease; no treatment had been taken for two months. She was poorly nourished and extremely weak. There was moderate tremor and exophthalmos. The thyroid gland (hyperplastic) was moderate in size and the basal metabolic rate was +45.

Antithyroid treatment in preparation for thyroidectomy was begun with propylthiouracil in a daily dose of 300 mg. A high caloric diet and supplemental vitamins were also prescribed. On the sixteenth day of treatment fever of 106°F. and severe sore throat developed. The leukocyte count was 600, with an absence of polymorphonuclear cells. Penicillin was promptly administered, with recovery of the patient. Leukocytes were normal in two weeks.

Since the patient was still a serious risk for thyroidectomy, weight 68 pounds and basal metabolic rate +25, it was decided to give further antithyroid treatment and as she had tolerated thiouracil for seven months this was chosen as the antithyroid drug. On the thirteenth day treatment was discontinued because of fever and sore throat and a polymorphonuclear percentage of 3. Penicillin was again administered and, because of fear of the presence of penicillin insensitive organisms, streptomycin was also given. The patient recovered with the white blood cells returning to normal in eight days.

This patient is now taking Lugol's solution and soon a final decision will be made as to whether or not additional measures are necessary to prepare her for safe thyroidectomy.*

* Since submitting this manuscript, this patient has had a two-stage thyroidectomy and has completely recovered.

SUMMARY

Reactions to propylthiouracil occurred in 13 of 672 patients (1.9 per cent), with ten of these reactions involving the blood, three leading to agranulocytosis. This experience indicates that propylthiouracil must be administered under careful supervision since serious reactions may occur following its use which need immediate treatment if complications are to be avoided.

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Acute Porphyr^a

Two Cases with Autopsy Reports

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THE name porphyria has a Greek derivation, *porphros*, meaning a crimson or purple color. In medical literature today it designates an obscure clinical entity involving "an inborn error of metabolism," as originally stated by Garrod. With a better understanding of the chemistry of the porphyrins, the classification of these abnormal conditions, in which various types of porphyrins are excreted, assumes a more rational form. The term *hematoporphyrin*, as first used by Gunther,⁸ is no longer accepted clinically in the strict sense, as it refers to a compound *hematoporphyrin* which does not occur in nature.^{10,14} The term *porphyria* is now accepted to designate the congenital type and the intermittent acute type of disturbed metabolism, characterized by the excretion of uroporphyrins in the urine. In congenital cases Type I isomer is found and the chromogen, *porphobilinogen*, is absent. Regarding acute porphyria, recent work by Watson and associates¹⁷ raises a question concerning the isolation of Waldenstroem's uroporphyrin III in pure form. They suggest that this may be a mixture of uroporphyrin I methyl ester and a heptamethyl ester, m.p. 208°. The term *porphyrinuria* includes those cases in which coproporphyrin Type I or Type III isomers are excreted in excess, secondary to certain other diseases or metabolic disturbances.^{15,18}

Congenital porphyria, as the name implies, is often manifested early in life and

occurs in males about four times as commonly as in females. The typical bullous eruption of the skin, referred to as *Hydroa aestivale* or *vacciniforme sue aestivale*, appears upon exposure to sunlight and may progress to scleroderma-like peripheral lesions. The dark colored urine and abnormal pigmentation of teeth and bones are also characteristic.⁹

In contrast to congenital porphyria, the acute type usually occurs between the second and fifth decades of life and is more common in women.¹⁵ The excretion of urine darkened by the presence of uroporphyrins and "porphobilin" (derived from the chromogen *porphobilinogen*) may occur intermittently, and is often associated with the clinical exacerbations. These episodes are typified by abdominal pain with nausea and vomiting, refractory constipation, neurological and psychotic manifestations and severe muscular pain. The abdominal symptoms may so closely simulate acute appendicitis or bowel obstruction that a laparotomy has been performed, and in many cases the vomiting may be so persistent that parenteral fluids are mandatory. The neurological symptoms, so aptly described by Waldenstroem,¹³ may assume such a variety of forms that he has applied to acute porphyria the epithet "*la petite simulatrice*." From his study of 143 cases, sixty of which had neurological symptoms, he stresses the frequency with which the mistaken diagnosis of hysteria is made. The

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variety of manifestations may range all the way from convulsions, quadriplegia, or delirium to subjective complaining and transitory paresis suggestive of psychoneurosis. A Landry's type of ascending paralysis is relatively common and may result in death from bulbar involvement. Hypertension frequently accompanies the acute episodes of porphyria.^{2,3,5,6,7,10,15}

Many cases have come to autopsy but there is considerable variance in reports of the pathology found, particularly regarding changes in the nervous system. Thus, in contrast to Berg's report³ of a normal brain and spinal cord in his case of a girl, aged twenty, Golden⁷ recorded leptomeningeal thickening, glial scarring, and "a patchy loss of ganglion cells in the cortex" of a forty-seven year old male. He characterized these changes as being indicative of a parenchymatous toxi-degenerative process. Mason⁹ demonstrated granular changes in the cortical nerve cells, degenerative alterations of the ganglion cells of the vagal and hypoglossal nuclei, and varying degrees of chromatolysis among the ganglion cells of the cord, particularly of the anterior horn in the lumbar area. The degeneration of the axis cylinders and myelin sheaths, with round cell infiltration, was most marked in the peripheral nerves of the lower extremities. He called attention to the lipoidal pigmentation, chromatolysis and vacuolization of the ganglion cells of the autonomie system, postulating a possible correlation with the gastrointestinal symptoms. These observations are in accord with those of Baker and Watson² who likewise describe moderate changes in the cerebral white matter and some degree of perinuclear and diffuse chromatolysis of the dorsal nucleus of the vagus and to a lesser extent of the facial and hypoglossal nuclei. They also noted that some of the muscle fibers had lost their striations and normal staining properties.

To date there is still no adequate explanation of the origin or point of action of the toxic substance which brings about the syndrome of intermittent acute porphyria. The chromogen porphobilinogen is apparently non-toxic, as large quantities have been isolated in a case during a remission.² However, the possibility that one of its derivatives, which include uroporphyrin and porphobilin, may play a rôle, must be kept in mind. Waldenstroem,¹³ on the other hand, observed a case in which during an acute attack, no porphyrins could be found in the urine.

Although liver damage has been demonstrable in several cases of porphyria,^{3,11} Mason and his group⁹ are led to believe that this organ plays no rôle in the etiology of the offending toxin. They assume that the production of uroporphyrin and excessive coproporphyrin may be the result of faulty hemoglobin metabolism in the bone marrow. In some there is a history of indulgence in a barbiturate such as sulphonal, trional or veronal, but in many instances such an exposure, with sensitivity, cannot be demonstrated, and one must fall back on a theory of endogenous intoxication or constitutional discrepancy. From clinical data and autopsy material available at the present time, it would seem that the nervous system is most vulnerable to this toxic agent, whatever its nature.

Hematoporphyrin has been injected experimentally into animals as reported by Rask and Howell.¹² Following dosages of 58 mg. per Kg. intravenously in dogs, a very striking sequence of events was produced, provided the animals were exposed to sunlight. Manifestations of cutaneous erythema and irritation, followed by motor excitation, hyperpnea and rapid pulse, led to a terminal stupor and death in circulatory collapse. From additional perfusion experiments on terrapin hearts they con-

clude that the central nervous system effects are reflex rather than the direct result of a toxic agent produced in the skin.

In very small doses for its stimulative effect, hematoporphyrin in the form of "Photodyn" has been used as a therapeutic agent in the treatment of depressive psychoses.¹

The two cases described below portray the typical clinical pattern ascribed to acute porphyria and the tendency to undergo remissions in spite of a poor ultimate prognosis.

CASE REPORTS

CASE 1. P. M. M., a twenty-seven year old girl, was first admitted to the Robert W. Long Hospital on March 5, 1945, because of extreme generalized weakness, difficulty in swallowing and occasional bowel incontinence. The initial symptoms of her illness, which began in October, 1944, had been psychic in nature, marked by a vague restlessness and emotional instability. Within a short time she became acutely ill with nausea, vomiting, abdominal pain and loss of weight. She was placed in an army hospital for two to three weeks, during which time there was noted a rapid loss of strength and impaired bowel function. She was transferred to Passavant Memorial Hospital in Chicago where, during a protracted stay of fourteen weeks, there had been an initial progression to complete quadriplegia with accompanying weakness of the right side of the face and difficulty in swallowing and talking. It had also been observed that the urine became a dark reddish color on standing and on demonstration of porphobilinogen, a diagnosis of porphyria was made. A gradual improvement in her condition then ensued, prior to her discharge early in March, 1945.

Physical examination at the time of her transfer to our hospital, revealed an individual in a poor state of nutrition with considerable muscular atrophy, weakness and pain in both upper and lower extremities. The temperature was 99.2°F., pulse 116, and blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The reflexia of her upper extremities were present and equal, but knee and ankle jerks could not be elicited. Aside from a diminution of sensation below the

elbows, the remainder of her examination was essentially normal.

Laboratory findings, during her stay in the hospital from March 5th through June 27th, showed a hemoglobin range from 10.5 to 12 Gm. The white blood cells varied between 5,000 and 8,000 with essentially normal differential counts. The serologic reaction (Mazzini) was negative and repeated sedimentation rates (Wintrobe) were 26, 37 and 24 mm. in one hour. Direct van den Bergh gave a delayed positive and the indirect showed 2.7 mg. of bilirubin. Urinalyses, aside from the dark color, were negative except for an occasional faint trace of albumin. The spinal fluid showed a white cell count of one, no red cells, negative globulin, sugar 80 mg. per cent, total protein 51 mg. per cent, and a gold curve of 10 zeros.

During hospitalization the patient was treated with hot fomentations to promote relaxation, accompanied later by tendon stimulation and muscle reeducation. She had recovered from the incontinence and regained her strength so that she could walk with support and could use her hands to write and to feed herself when she was discharged the latter part of June, 1945. This improvement had continued when she was seen in our out-patient department in August, 1945, and again in January, 1946. Two weeks after her last visit she became actually ill with nausea and vomiting, fever, low abdominal pain and obstipation for five days. A laparotomy, performed at her local hospital, revealed a ruptured appendix with peritonitis. Her postoperative course was stormy and during her convalescence there was a recurrence of generalized weakness and pain in her extremities, accompanied finally by persistent vomiting. She was readmitted to our hospital on May 28, 1946, because of her alarming nutritional state. Upon examination one was impressed by the extreme degree of cachexia and debilitation. She could not speak above a low whisper but her faculties were unimpaired. At this time her temperature was 100.3°F., pulse 120, and blood pressure 138 mm. Hg systolic and 110 mm. Hg diastolic. There was almost complete flaccid paraplegia with pronounced muscle atrophy and a large decubitus ulcer was present over the sacrum. The abdomen was slightly distended

and tender to palpation but auscultation revealed scattered bowel sounds. The white blood count was 15,300 with 17 band cells, 65 neutrophils, 17 lymphocytes and 1 monocyte. Blood non-protein nitrogen was 21 mg. per cent. The urine was consistently dark colored, often with a reddish tinge, and was strongly positive for porphobilinogen by the test of Watson and Schwartz.¹⁶ She was given parenteral fluids, supportive treatment with vitamins, and penicillin, with no response. She suffered from persistent nausea and vomiting and almost constant muscular pain. Her pulse remained elevated between 115 and 140 and her temperature reached 100 or 101°F. almost daily. Her downhill course was terminated by death in respiratory failure on June 12, 1946.

An autopsy was performed and gross examination revealed the presence of consolidation and edema in both lungs and a generalized acute peritonitis. Upon histological examination the following pertinent abnormalities were noted: The acini of the thyroid were compressed by a connective tissue stroma into which had infiltrated many lymphoid cells. In some areas all traces of colloid were obliterated, warranting a microscopical diagnosis of stroma lymphomatosa. Neurotrophic degeneration of skeletal muscle was manifested by variation in size of individual fibers and loss of cross striations. The cortical white brain substance revealed a moderate deposit of yellow pigment in the perivascular structures, particularly in the frontal lobes. In the spinal cord the neurone bodies of the anterior horn cells showed some tendency toward shrinkage and pyknosis. Sections of the peripheral nerves manifested the most constant and severe alterations; nerve bundles were irregular in outline and shrunken, and there was marked demyelination.

It is of interest to note that the younger sister of this patient is afflicted with acute porphyria, though of a milder degree without neurological manifestations. At the age of twenty-four, in 1944, she had an episode of protracted nausea and vomiting which was relieved following the administration of parenteral fluids. A second attack, similar

to the first, occurred in March, 1946, at which time she was told porphyrins were found in the urine. She made a good recovery without symptoms of paralysis. A specimen of urine checked in our laboratory revealed the presence, in abundance, of porphobilinogen, thus substantiating the diagnosis.

CASE II. E. L., a twenty-six year old housewife, was admitted to the Robert W. Long Hospital on February 2, 1942, complaining of a burning sensation in the suprapubic region of one week's duration, urinary frequency, nausea and vomiting. In April of 1940, because of low abdominal pain, an appendectomy had been performed. During her postoperative course, which was complicated by cystitis, it had been noted that her urine became a deep brown color on standing. In the past two years she had felt well and there had been no recurrence of abdominal distress, although the color change in the urine had persisted. Renal function tests in March, 1941, were within normal limits.

Physical examination revealed a relatively slender individual, suffering from considerable discomfort, but not acutely ill. The temperature was 99.3°F., pulse 90, and blood pressure 110 mm. Hg systolic and 90 mm. Hg diastolic. The only pertinent findings included tenderness to pressure over the bladder area and both costo-vertebral angles. The heart was of normal size, there were no murmurs present and the rhythm was regular. The lungs showed no demonstrable abnormality. Reflexia were present and physiological.

Laboratory findings showed that repeated urinalyses frequently contained red blood cells, many pus cells and a trace of albumin. Urea clearance, checked in March, was 34 per cent of normal. Blood studies, during her hospital stay: hemoglobin ranging from 11 to 14 Gm; white blood cells as low as 3,000, but usually between 6,000 and 7,000, with normal differential counts; sedimentation rate (Wintrobe) 21 mm.; and serology (Klein and Mazzini) normal. Spinal fluid showed a normal pressure, no cells, sugar 74 mg. per cent, total protein 22 mg. per cent, and a gold curve of 10 zeros.

Estimation of liver function by galactose tolerance test gave an excretion of 3 Gm. of galactose in five hours. Following intravenous administration of bromsulphthalein, 85 per cent of the dye was retained outside the blood after sixty minutes. The icteric index was 6, and both direct and indirect van den Bergh were negative. Special examination of the urine revealed the presence of uroporphyrin Type III as determined on a basis of its solubility and fluorescent properties by methods referred to by Dobriner and Rhoads.⁴

Because of the severe degree of cystitis present, a catheter was anchored for frequent lavage and she was given sulfathiazole by mouth. She first complained of muscular weakness and an aching sensation in her arms and thighs on March 7th. This became progressively worse so that within a week she was unable to hold a glass of water or feed herself. Concomitantly she developed a marked degree of despondency and discouragement. On March 19th, neurological examination revealed absent biceps, triceps, pronator, and supinator reflexes bilaterally, hypoactive knee jerks and normal ankle jerks. She was allowed to go home for a furlough but returned within ten days because of increasing muscular weakness and pain, difficulty in swallowing and abdominal discomfort. Following readmission her course was progressively downhill. Her blood pressure varied between 105/75 and 120/100. Difficulty in phonation and swallowing became more marked prior to her death on June 7, 1942.

The autopsy report showed that the only gross pathological condition was bilateral pulmonary congestion. Microscopically, the following pertinent pathological changes were noted: The liver showed severe albuminous degeneration and passive congestion. Sections of the spleen revealed an early amyloidosis. No significant changes were observed in the spinal cord, but degeneration of the myelin sheaths in the right sciatic nerve could be demonstrated. Permission for examination of the brain was not obtained.

SUMMARY

Two cases of acute porphyria are described with particular reference to the general course of the disease and to the

findings demonstrable at autopsy. Both cases were characterized by rather typical exacerbations and remissions of symptoms referable primarily to the nervous system and to the gastrointestinal tract. The familial tendency was demonstrated in the first case. Histological study of tissues revealed the most significant changes in the peripheral nerves in which demyelination was the outstanding feature. Loss of striations in skeletal muscle accompanied the neurological abnormalities. The identity and source of this toxic agent, as well as an interpretation of the pathogenesis of this type of disturbed metabolism, is still being sought.

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Spontaneous Mediastinal Emphysema and Pneumothorax

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DRAMATIC in onset, alarming in subsequent manifestations yet in the great majority of instances carrying an excellent prognosis, spontaneous mediastinal emphysema and spontaneous pneumothorax, whether occurring independently or in association, offer an arresting problem to the diagnostician. The two disorders may be considered together so alike are they in their presumptive etiology, symptomatology and clinical course. Indeed, the case to be presented is but one of many in the literature in which the two disorders have occurred together.¹⁻¹⁵ The subject is important for several reasons: The conditions are more common than hitherto suspected and lend themselves to confusion with far more serious afflictions. Last, they of themselves are relatively harmless, a fact which if generally appreciated would save many man hours of work and many anxious reflections.

CASE REPORT

On August 3, 1946, Dr. J. G., a twenty-three year-old dentist, was seized with a severe stabbing pain in the lower left chest near the sternum which awoke him from a sound sleep. Except for working rather late at his office he had undertaken no unusual exertion during the preceding day nor did he recall any respiratory infection. The pain increased in intensity during the next twelve minutes, radiating through to his back, beneath the left shoulder blade and thence up to the suprascapular region. Deep breathing or coughing greatly accentuated the pain, and the patient found it necessary to sit in a semi-upright position in order to get his breath. He was seen almost immediately by his family physician who was unable to detect

any changes in heart or breath sounds. One-half gr. of morphine during the next eight hours was almost entirely ineffective in controlling the pain. After the physician left the patient was startled to hear a loud clicking sound emanating from his left chest. Lasting for nearly two hours, the clicking was said to be audible halfway across the room. Next morning, some eight hours after onset of the illness, the patient was hospitalized for study.

Following an unusually heavy day's work a year and a half ago, the patient suffered a sudden attack of severe pain in the left chest radiating through to his back in the manner of the present attack. Several hours after onset of the pain he heard a loud clicking noise, apparently originating in his left chest. For twenty-four or thirty-six hours after beginning the pain continued to be severe and was made worse by abrupt changes in body position. Nevertheless the patient continued work and it was not until two weeks had gone by that he consulted his doctor. Once home he was hospitalized and given a two weeks' course of penicillin for pericarditis. At that time a rough to-and-fro murmur was audible over the apex of the heart; the murmur was doubtless considered a pleuro-pericardial friction rub. Chest x-ray showed only a small calcified Ghon lesion near the hilum of the left lung. There was no evidence of constitutional disturbance, such as fever, tachycardia or leukocytosis, throughout the hospital stay. Following his discharge, the patient remained asymptomatic, partaking of vigorous sports such as hunting, fishing, running and cycling, all without noticeable handicap.

In 1943 the patient had severe pain in the left chest for about twelve hours. He remained in bed a day or two but continued his duties thereafter. There was no past history of rheumatic fever or scarlet fever. The patient recalls no trauma to the chest. Frequent x-rays of the chest over the past few years disclosed no evi-

dence of tuberculosis. Yearly tuberculin tests had been weakly positive.

Physical examination showed a well developed, well nourished, somewhat slender, young, white man in no distress as long as he remained propped in a semi-upright position. Changes of position, however, caused him to grimace with pain. The temperature was 98°F., pulse, 80, respirations, 24 and blood pressure, 106/70. Findings of interest were confined to the chest. Breathing was shallow and respiratory excursions were generally limited but no asymmetry was detected. Upon percussion there was hyper-resonance over the sternum and adjacent precordial region. The heart borders could not be accurately mapped out. Auscultation of the chest revealed diminished breath sounds and vocal fremitus over the left chest posteriorly down to about the sixth rib. Over the precordium extending from a point just to the right of the sternum around to the posterior axillary line could be heard a peculiar, harsh clicking sound, synchronous with systole, which resembled pebbles dropped in a metal bucket. The patient himself listened to the sound and avowed it was the same as that he heard the night before. The heart sounds proper were somewhat faint but otherwise normal in quality, and there was no evidence of cyanosis, venous engorgement or mediastinal shift.

Laboratory studies on admission showed a white count of 8,800 with a normal differential count. Subsequent hematologic studies were well within normal limits. X-ray and fluoroscopy of the chest made twelve hours after onset of the present illness revealed a large area of pneumothorax on the left, principally affecting the upper lobe which was almost entirely collapsed. There was no displacement of the mediastinum nor was air visualized within that structure.

Bed rest, sedation and occasional doses of pantopon constituted the only measures instituted for therapy. Second strength PPD, injected intracutaneously, showed a weakly positive reaction. Sedimentation rate was normal.

Except for rather severe, right lower quadrant pain for two or three days following hospital admission, the patient pursued an uneventful course. On the eleventh day x-ray showed virtually complete re-expansion of the left lung. The patient was discharged on the fourteenth day without specific recommendations other than to keep the glottis open at all times,

especially when any strenuous exertion was undertaken.

Definition. For the purposes of this paper spontaneous is taken to mean arising without apparent cause in presumably healthy individuals in whom no underlying pathologic condition is subsequently demonstrated. Although emphysema has been defined as "the presence of air in the interstices of the connective tissue of a part,"¹⁶ its use in the present context, mediastinal emphysema, has been to indicate the presence of free air in the mediastinum. Pneumothorax,¹⁷ after Taschman, represents the condition in which air is present in the pleural cavity.

Rather rigid definitions have been adopted in the hope that subsequent confusion will be avoided. Spontaneous mediastinal emphysema, for example, has been described in patients undergoing labor,¹⁸ in the newborn¹⁹ and in asthmatics²⁰ while spontaneous pneumothorax, of course, has been observed in many infectious processes of the lungs²¹ as well as in congenital cystic disease,²² bronchiectasis²³ and even malignancy.²⁴ The present report does not include such cases.

Incidence. The incidence of spontaneous mediastinal emphysema is difficult to calculate in that only forty-two cases, including the one presented here, have been reported.^{1-15,25-34} Hamman stated as far back as 1939,³ however, that more and more physicians had reported to him personally concerning recognition of the condition. It is probable then that the condition is much more common than figures based upon the literature would indicate.

Spontaneous pneumothorax appears to be far more prevalent. Blackford³⁵ found fifteen cases in three years in Virginia college students while Wilson³⁶ found eleven in a four-year period at Yale. Schneider,³⁷ at the induction station in Grand Central Terminal, states that 1/500 of the inductees gave a verifiable history of pneumothorax. An estimate of 1-1,000 in the young adult male population would probably not be far wrong.

Age. Both spontaneous mediastinal emphysema and spontaneous pneumothorax are notably confined to young people. Inasmuch as a summary of the cases of the former condition has not thus far appeared in the literature, the author has charted them in detail with respect to age, a policy followed in other matters pertaining to mediastinal emphysema. (Table I.)

A breakdown of the 199 cases of spontaneous pneumothorax reported by Ornstein,²¹ Wilson,³⁶ Schneider,³⁷ Blackford,³⁵ Leggett³⁸ and Goldman³⁹ reveals that 94 per cent of the patients were between the ages of fifteen and forty years.

Sex. The male sex is predominantly favored by both diseases. Using the same sources for our figures as for age, we find only two females with spontaneous mediastinal emphysema and three with pneumothorax.

History of Effort. In Table I the judgment as to whether or not the patient had undergone "none to slight" exertion was somewhat difficult. Any customary activity not commonly regarded as strenuous was termed slight, such as walking home from work,³ driving a car³ or even servicing a mortar.¹⁵ Of the five cases listed as those performing moderate to severe exertions, running one-half a mile,²⁵ cycling,²⁵ performing military calisthenics,¹⁵ swimming¹⁵ and, perhaps unfairly in the case of a seventeen year old girl, dribbling a basketball⁵ were included.

According to Ornstein,²¹ only 22 per cent of his patients gave a history of exertion while Schneider³⁷ reported such a history in 30 per cent. In twenty-three of thirty-nine cases (59 per cent) completely reported by Cohen and Kinsman⁴⁰ there was no provoking cause; ten soldiers (26 per cent) had undergone mild exertion, such as walking. At all events, if these cases (186) are representative a history of exertion in spontaneous pneumothorax is present in less than one-third of the cases.

ETIOLOGY

Pulmonary tuberculosis was long considered the chief causal factor in the large

majority of cases of spontaneous pneumothorax. Biehl,²³ who is representative of the older writers on the subject, gave an estimate of 80 per cent. After the report, in 1932, of Kjaergaard,²² who found tuberculosis in only one of forty-nine cases, a

TABLE I
SPONTANEOUS MEDIASTINAL EMPHYSEMA

Age (in yr.)	Cases	Per Cent
15-19.....	6	14
20-29.....	26	62
30-39.....	5	12
40-49.....	1	2
50-59.....	2	5
* Unlisted.....	2	5
Total.....	42	100

Sex	Cases	Per Cent
Male.....	40	95
Female.....	2	5
Total.....	42	100

Exertion	Cases	Per Cent
None to slight.....	37	88
Moderate to severe.....	5	12
Total.....	42	100

* Medical student; ⁴ lawyer.²³

flood of contrary estimates was released. Perry⁴¹ found tuberculosis in 6 of 250 cases; Ornstein,²¹ in three of fifty-eight and Schneider,³⁷ in one definitely and two problematically of one hundred cases—an overall incidence of 3 per cent in 470 cases. Active pulmonary tuberculosis was observed in two (5 per cent) of the cases reported by Cohen and Kinsman.⁴⁰ In addition to the clinical statistics militating against the culpability of tuberculosis in spontaneous pneumothorax, Hamman⁴² provides further negative evidence in the pertinent observation that pneumothorax

in tuberculous patients is a dramatic event attended by a violent reaction of the pleura and definite constitutional symptoms. When such is not the case, pursues Hamman, pneumothorax must be regarded as due to the same mechanism as in the healthy. Last, tuberculosis has not been found in the few postmortems done in clinical cases of spontaneous pneumothorax.

Although uncommon, spontaneous pneumothorax has been known to occur in congenital cystic disease of the lung,²² in bronchial asthma,⁴³ bronchiectasis,²³ and even malignancy.²⁴ Such conditions, however, hardly meet our criterion of "spontaneous," absence of demonstrable underlying pathology.

Ornstein²¹ has advanced a rational and widely accepted explanation of pneumothorax. The time-honored theory of "ruptured emphysematous bleb" had not been well supported by postmortem evidence, nor had cases of pneumothorax been observed in those, especially the elderly, who suffered from emphysema. Why, wondered Ornstein, did spontaneous pneumothorax occur almost exclusively in healthy young males? Why, again, was there so seldom a history of effort in these patients? Under the fluoroscope Ornstein observed that the apices of the lungs could be seen to "light up" when in full inspiration the glottis is closed and the thoracic and abdominal muscles compressed, just the condition during coughing or strenuous effort. Air is driven from the lung bases to the apices which become markedly distended. This forceful inflation, reasoned Ornstein, could easily overdistend and rupture the elastic fibers of the subpleural alveoli, especially at the apex. The result would be the formation of a subpleural bleb. If, by some such mechanism as a check valve which would admit air to the bleb but prevent its egress, the bleb grew increasingly distended, eventual rupture would occur with the patient at rest. A check valve of the sort envisaged has actually been observed by Kjaergaard.²² The first mechanism thus outlined would explain the incidence in

healthy young males who are usually given to severe exertions. The second goes far to explain why pneumothorax so often occurs when the patient is at rest. Since circumstances favorable for study are very seldom obtained so rarely does death ensue, any etiologic concept must remain largely theoretical. Ornstein's appears to be the best of the present explanations.

The pathologic physiology of spontaneous mediastinal emphysema is similar and possibly related to that of pneumothorax. Macklin⁴⁴ has shown experimentally in cats and rabbits that when air under a pressure of from 1 to 22 mm. Hg is forced through a truncated catheter introduced into the right lower lobe bronchus, distention and rupture of the alveoli follow. The air thus released into the pulmonary interstitial tissue dissects along the sheaths of the pulmonary vessels to the lung roots. The pressure gradient from the alveolus to the vascular sheath is said to be the direct result of overdistention which pulls away the enveloping alveolus from the vessel sheath.⁴⁵ Once at the lung roots the air forms large blebs in the sheaths of the pulmonary vessels. When the pressure is great enough, the air ruptures into the mediastinum. Still greater pressure results in pneumothorax and subcutaneous or retroperitoneal emphysema, respectively. In the animals showing Hamman's sign bubbles of air were observed between the anterior pericardium and thoracic cage. Careful examination of those cases with pneumothorax disclosed no evidence of a tear in the visceral pleura of the lungs. In many cases, however, rents in the thin mediastinal wall were observed.

Hamman⁴² believes that Macklin's experimental findings obtain in human cases of spontaneous mediastinal emphysema, the sequence of events being first rupture of the alveoli lying on interstitial bands of connective tissue, then entrance of the air into interstitial tissues and dissection along the sheaths of the pulmonary vessels where it escapes into the mediastinum. Free air in the mediastinum is gradually absorbed although why it is confined there is not

fully understood. A great amount of air will escape because of pressure, usually into the pleura. In exceptional cases subcutaneous or retroperitoneal emphysema result.

To go further Hamman postulates that many cases of spontaneous pneumothorax might arise from the same cause. Macklin's failure to find tears in the visceral pleura of his experimental animals is cited as evidence. Again, pneumothorax and mediastinal emphysema are often found in association. A review of the forty-two spontaneous cases of mediastinal emphysema reveals associated pneumothorax in 55 per cent of the cases. While this incidence is high enough to be suggestive, two points must not be overlooked. First, mediastinal emphysema has not been observed in the vast majority of cases of spontaneous pneumothorax. Second, in all the cases in which the two conditions were associated the pneumothorax was on the left side. The reports on spontaneous pneumothorax show that the accident is equally common on the right. Of Schneider's one hundred cases, for example, fifty-five were right-sided, forty-four left-sided and one was bilateral³⁷ while Cohen and Kinsman⁴⁰ report 54 per cent of their cases as right-sided and 46 per cent left-sided. Although as Hamman testifies there is no theoretical reason why the pneumothorax in cases of mediastinal emphysema should be on the left, the fact that in all reported cases the lesion has been left-sided cannot be lightly dismissed. The middle way is taken by McGuire and Bean⁵ who state that in interstitial emphysema of the lungs resulting from a rupture of alveoli, the air may travel along interstitial bands toward the hilum and enter the mediastinum or else, more commonly, it might pass outward directly to the pleura where it forms a bleb. The latter eventuality, while it is at variance with the pressure gradients observed by Macklin, closely parallels the theory of Ornstein. At all events the theories propounded to explain the pathogenesis of spontaneous mediastinal emphysema and

spontaneous pneumothorax are closely allied.

SIGNS AND SYMPTOMS

Pain is the chief complaint in nearly all cases of spontaneous mediastinal emphysema.

TABLE II
SPONTANEOUS MEDIASTINAL EMPHYSEMA—ANALYSIS OF
FORTY-TWO CASES

Symptoms	No. Cases	Per Cent
1. Chest pain	40	95
2. Dyspnea	12	29

Signs	No. Cases	Per Cent
1. Peculiar sound over heart	38	90
2. Diminution of cardiac dullness	14	33
3. Absence of constitutional symptoms	38	90
4. Subcutaneous emphysema	10	24

X-ray Findings	No. Cases	Per Cent
1. Air in mediastinum	16	38
2. Pneumothorax	23	55

sema. (Table II.) In the two cases^{32,34} in which pain was absent the first manifestations were emphysema of the scrotum and pneumoperitoneum but these were not truly uncomplicated cases. Usually severe, sharp and stabbing, the pain begins in the precordial and substernal region and radiates through to the back, up into the left shoulder and side of the neck and, at times, down the left arm.⁴ Changes of position, coughing or even swallowing tend to accentuate the pain.³ It lasts as a rule for many hours before diminishing in severity. At times the pain may begin in the left side of the chest before shifting to the substernal region. In such instances interstitial emphysema of the lungs precedes pneumomediastinum.⁴⁵

The chief associated symptom is dyspnea which has been recorded in twenty-nine instances. Owing to accentuation of the pain by respiration, some degree of dyspnea may result from mere "splinting" of thoracic movement. In some cases, however, enough air may be trapped in the mediastinum to cause embarrassment to the vital structures therein. Should this state become pronounced, with venous engorgement, cyanosis and circulatory collapse, immediate and heroic measures must be undertaken for relief. Such have not been necessary in the spontaneous cases thus far reported.

Onset of spontaneous pneumothorax as a rule is characterized by sudden, sharp, severe pain localized over the affected lung which may extend to the shoulder, neck, back and even the abdomen.^{17,40} The author has seen one case which simulated an acute abdominal catastrophe. Changes of position and deep respiration markedly accentuate the pain. Even riding in a car might make the pain almost unbearable. A small minority of patients, however, may be unaware of the condition which has been discovered by Schneider,³⁷ Wilson³⁶ and Blackford³⁵ upon routine x-ray. Duration of the pain, as in mediastinal emphysema, is a matter of hours. Some measure of relief is obtained by bed rest.

Dyspnea and cyanosis are often observed in spontaneous pneumothorax, their severity being in rough proportion to the degree of collapse of the affected lung. They arise, according to Ornstein,²¹ from three causes: immobilization of the thorax from pain, poor aeration of the venous blood in the collapsed lung, the circulation of which becomes negligible after the first twenty-four hours, and actual loss of vital capacity due to pneumothorax. When seen immediately after onset, these patients may show signs of shock, with pallor, sweating, rapid pulse rate and decline in blood pressure. A slight reflex cough is commonly observed in the early stages.^{17,21} Should any of these associated symptoms be pronounced one must suspect tension pneumothorax and

take appropriate measures for immediate relief.

The most distinctive clinical sign in mediastinal emphysema is the peculiar sound heard over the heart. (Table II.) Known as Hamman's sign³ it has been described as a "crunching, crackling, clicking, bubbling or churning noise" synchronous with the heart beat. Other authors have added colorful descriptions, including the "rattle of dried peas on taut canvas,"²⁵ "the wrinkling of a newspaper"²⁵ and "the grinding of gears."¹¹ Whatever the descriptive phrase chosen by the individual writer, all agree that once heard the sound is never forgotten. It cannot, as Stein¹³ emphasizes, be confused with any other condition nor does it occur in any other condition. Adcock³² has heard in four patients shortly after induction of artificial pneumothorax a very loud, single, slapping sound synchronous with systole but usually audible only in one phase of respiration with the patient lying on the left side. In mediastinal emphysema, by contrast, one hears a crackling and crunching throughout the respiratory cycle. Greene³¹ writes that a knocking, tapping or metallic sound may accompany left pneumothorax but that bubbling, crunching or clicking noises indicate emphysema of the pulmonary interstitial tissues or the mediastinum. In late or transitional stages, however, as Miller¹⁵ warns the sound may resemble a rough pericardial friction rub. Of interest and distinct help in diagnosis is the fact that of the thirty-eight patients in whom Hamman's sign was detected twenty-one, or 55 per cent, heard the sound themselves.

Diminution or obliteration of cardiac dullness upon percussion has been reported in about one-third of the cases of mediastinal emphysema. (Table II.) When present this is a virtually pathognomonic sign.

Absence of constitutional symptoms provides negative evidence of inestimable value in differentiating mediastinal emphysema from more serious disorders, such as myocardial infarction, pericarditis, pulmonary

embolism and dissecting aneurysm of the aorta.^{13,15} In only four cases has fever of over 100°F. been reported; at least three of these had complicating disorders.^{3,32,34} Systemic manifestations, such as tachycardia, fall in blood pressure, leukocytosis or increased sedimentation rate do not occur.

Subcutaneous emphysema of the neck or outer chest wall, detected by observation of swelling and crackling to the touch in these tissues, affords conclusive evidence of mediastinal emphysema.³ It has been reported, however, in only one-fourth of the cases.

The signs of spontaneous pneumothorax may be summarized as follows:³⁶ respiratory lag on the affected side; slight increase in resonance over the affected area; diminished to absent breath sounds and vocal or tactile fremitus and, possibly, displacement of the mediastinum away from the affected side. Inasmuch as they are just what we should expect in view of the underlying pathologic condition, these signs do not require much discussion. It is worthy of emphasis, however, that diagnosis of pneumothorax by physical signs alone is many times exceedingly difficult. The air might represent but a thin sheet interposed between the lung and chest wall, in which event slight dullness instead of hyperresonance results. Tympany, although mentioned in most of the textbooks, is, as Wilson says,³⁶ seldom observed. Air under pressure is more likely to give a wooden or flat note to percussion. The coin sound and succession splash do not occur in uncomplicated pneumothorax.

X-ray Findings. Air within the mediastinum has been roentgenographically demonstrated in 38 per cent of the reported cases of spontaneous mediastinal emphysema. In the anteroposterior view the characteristic finding is a thin line of density parallel to the border of the heart, usually the left border.³ Lateral views may show air pocketed between the anterior border of the heart and the chest wall. Oblique views are valuable in revealing air in the posterior mediastinum. All three views should be taken in cases of suspected

mediastinal emphysema. Positive x-rays afford incontrovertible proof of the diagnosis.

A review of the cases of spontaneous mediastinal emphysema shows that in twenty-three cases, 55 per cent, left pneumothorax was present upon x-ray. Although usually small³³ and confined to the apical portion, the area of pneumothorax may be large, causing 40 to 75 per cent collapse of the affected lung.¹⁵

The outstanding finding in spontaneous pneumothorax is, of course, presence of air in the pleural cavity. Wilson³⁶ as well as Greenberg⁴⁶ emphasizes that air may be missed in mild cases unless a film is taken at expiration. Rarely will a lateral film show pneumothorax in those patients in whom the collapsed lung is plastered against the posterior wall of the pleural cavity. Fluoroscopy alone, as Blackford warns,³⁵ is not a reliable method of demonstrating pneumothorax. Atelectasis is always present to some degree, usually involving the upper lobe of the affected lung. According to Taschman,¹⁷ a large degree of collapse is the general rule but Ornstein²¹ reports forty-one of his fifty-eight cases (70 per cent) as "slight." Displacement of the mediastinum, heart, great vessels and trachea may be observed in pronounced cases.

A small amount of fluid is observed in the costophrenic sinus in about one-half of the patients with spontaneous pneumothorax.²¹ Any measurable quantity of fluid should arouse strong suspicions of tuberculosis or, much more rarely, of hemothorax.

Adhesions are rarely observed in spontaneous pneumothorax.^{17,21} Of the five patients showing adhesions observed by Cohen and Kinsman⁴⁰ one had active and two had inactive tuberculosis. Their presence leads one to suspect tuberculosis.

Diagnosis. "Any diagnosis is easy," the late Soma Weiss used to say, "if you can think of it"! Sudden onset of severe chest pain in a previously healthy young male should always bring to mind the possibility of spontaneous pneumothorax or mediastinal emphysema. Careful examination

of the patient will nearly always, in the latter case, disclose the peculiar sound over the heart often accompanied by diminution of cardiac dullness. In the former, efforts should be made to elicit presence of air in the pleural cavities. Whenever possible, x-ray should be taken to provide confirmatory evidence.

The striking absence of constitutional symptoms in the two disorders makes the exclusion of more serious disorders relatively easy and certain. Myocardial infarction, pericarditis, pulmonary embolism, dissecting aneurysm of the aorta and acute abdominal catastrophes are rarely unaccompanied by fever, disturbances of pulse rate or blood pressure, leukocytosis or elevated sedimentation rate. Although many small pneumothoraces are doubtless misdiagnosed as pleurisy, intercostal neuralgia, muscle strain and the like,³⁵ such errors can be avoided by careful physical examination and more liberal use of roentgenography.

Tuberculosis must be ruled out in patients with spontaneous pneumothorax. Reliance upon statistics alone, although reassuring, is indefensible when one is dealing with an individual case. Here again the absence of constitutional symptoms is of prime importance. The presence by x-ray of adhesions or more than a small quantity of fluid puts the burden of proof upon him who says tuberculosis is not present; prolonged observation with frequent sputum examinations and cultures, including those from gastric washings, should be carried out in such cases. Even in adults the tuberculin test has proved valuable; when it is negative, the odds are strongly against tuberculous infection.^{38,47}

TREATMENT

Treatment of both spontaneous mediastinal emphysema and spontaneous pneumothorax is, in all but rare cases, "masterful inactivity."⁴⁸ Bed rest and sedation together with opiates suffice for those with severe cases. Cohen and Kinsman⁴⁰ advocate the use of oxygen for severe dyspnea. The length of time that a patient should remain

in bed is still being debated. Those who specialize in tuberculosis advise at least four weeks' bed rest;^{17,21} others, such as Blackford³⁵ and Perry,⁴¹ believe two weeks to be enough. Since re-expansion of the lungs takes place in most cases within two weeks and since the patients affected are healthy young males, the shorter period would seem sufficient.

Amounts of air large enough to cause circulatory or respiratory embarrassment should be aspirated. In the case of mediastinal emphysema this operation may be performed either by insertion of a hollow curved needle into the mediastinum or, especially when subcutaneous emphysema of the neck is present, by incision through the jugulum.³³ Such contingencies have not arisen in the reported cases of spontaneous mediastinal emphysema. Pneumothorax of the "tension" type is aspirated by use of the conventional apparatus for giving artificial pneumothorax, with the bottles reversed, by attaching flexible tubing to the chest needle and submerging the other end in a jar of water or even by use of a simple needle and syringe outfit.¹⁷ It must be emphasized, however, that the collapsed lung in spontaneous pneumothorax is in the ideal condition for repair. Drawing off air during the first three days after onset serves only to increase the size of the hole in the visceral pleura, with resultant delay in recovery.³⁶ Even in tension pneumothorax Hennell and Steinberg⁴⁹ advise avoidance of aspiration; the patient is given sedatives and instructed to lie on the affected side. In patients with bilateral pneumothorax great judgment must be exercised in the performance of aspiration in order to maintain a balance between the two sides. The needles should, according to Taschman,¹⁷ be left in some time.

In the uncommon but ominous complication of hemopneumothorax the blood must be aspirated and partially replaced by air lest further bleeding be encouraged.³⁹ One must insist on rigid enforcement of bed rest.

Prognosis. When life is concerned, the prognosis either of mediastinal emphysema

or of pneumothorax, when spontaneous in origin, is excellent. Although the rare bilateral pneumothorax is said to carry a mortality rate approaching 50 per cent³⁵ and hemopneumothorax to cause fatalities in from 16 to 37 per cent of reported cases,^{35,36} those with uncomplicated cases invariably recover. Emphasis must be placed on complete recovery for many patients can thereby be spared undue alarm and unnecessary anxiety. There is a word of caution to be said: Pneumothorax is recurrent in about 25 per cent of the cases;^{21,36,37,40,49} eleven patients of the forty-two reported cases of mediastinal emphysema (26 per cent) have suffered recurrences.^{4,7,9,13-15,25,30,33} Five patients (12 per cent) suffered pneumothorax as distinct from that observed in association with mediastinal emphysema.^{3,4,7,33} The patient should be informed then that there is a definite likelihood of recurrence yet there is small need for anxiety on that score. After the age of thirty recurrences are exceedingly rare. Kjaergaard²² and later Hennell and Steinberg⁴⁹ have successfully treated patients with multiple recurrences by inducing, by means of sclerosing solutions, a sterile pleuritis. Such a procedure, however, is seldom indicated.

SUMMARY AND CONCLUSIONS

A case of spontaneous mediastinal emphysema with left pneumothorax is presented.

Spontaneous mediastinal emphysema and spontaneous pneumothorax are benign disorders which predominantly affect young men. Theories regarding the etiology of the two conditions are closely allied. Both are chiefly characterized by sudden onset of severe pain in the chest in the previously healthy. Careful examination of the chest, supported by roentgenographic studies, will nearly always reveal the diagnosis. Valuable confirmatory evidence is afforded by failure to detect signs of a systemic disturbance.

Therapy is principally supportive although aspiration of trapped air may be indicated in those with severe cases. While

recurrences are common, the prognosis in uncomplicated cases is uniformly good.

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Pyoderma Gangrenosum in Chronic Non-specific Ulcerative Colitis*

A Report of Three Cases

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DERMATOLOGIC complications are not uncommon in patients with non-specific ulcerative colitis. The incidence varies from 2.45 per cent in Bergen's¹ series to 10.7 per cent in the group reported by Ricketts and Palmer.² Among the cutaneous manifestations the pyogenic lesions are particularly important because of their marked resistance to treatment and the prolonged disability of the patient. Pyoderma gangrenosum represents the most severe of the cutaneous suppurative complications. This condition is characterized by pustular lesions which tend to break down, to ulcerate and to extend in all directions. The ulcers discharge foul smelling, purulent material. They may be so extensive as to result in massive necrosis of large portions of the integument. A variety of bacteria, especially staphylococci, streptococci, *Bacillus pyocyaneus*, *B. necrophorum* and *B. coli*, have been cultured from the lesions. The ulcerations typically are resistant to almost all forms of therapy. Healing proceeds slowly and with residual atrophic scarring. Any portion of the skin may be involved; however, involvement of the face apparently is rare.

Pyoderma gangrenosum occurs usually as a complication of chronic debilitating illnesses, and its development seems to be related to the poor nutritional state of the patient and his decreased resistance to infection. Of the five cases described by Brunsting, Goeckerman and O'Leary³ four had chronic non-specific ulcerative colitis

while the fifth patient had empyema. Jankelson and Marshall,⁷ Lanc,⁴ Cohen,⁵ Cowet,⁶ Jankelson and Massell,⁷ Jankelson and McClure,⁸ Mintzer⁹ and Brooke¹⁰ also have reported pyoderma gangrenosum as a complication of non-specific ulcerative colitis. Felsen^{10,11} has recorded its appearance in patients with bacillary dysentery.

The purpose of this paper is to indicate the importance of pyoderma gangrenosum as a complication in three patients with chronic non-specific ulcerative colitis. In Case 1 the pyoderma was so severe and resistant to therapy that it assumed primary significance in the prolonged disability of the patient.

CASE REPORTS

CASE 1. M. R., No. 97682, a forty-seven year old housewife was first seen in January, 1934. She had been troubled with "constipation" for many years, but also had experienced episodes of diarrhea following excessive ingestion of fresh fruits and vegetables. Diarrhea recurred two weeks before admission, with the daily passage of as many as fifteen to thirty loose stools containing mucus and blood. There was marked rectal tenesmus with abdominal cramps and distention. There had been a weight loss of 10 pounds. No significant abnormalities were detected on physical examination. Proctoscopic examination revealed numerous small ulcerations and bleeding points of the rectal mucosa. Routine laboratory studies were normal; the Wassermann test was negative. Examination of one stool specimen was negative for *Endameba histolytica*. Roentgen examination of the colon

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demonstrated a marked irritability of the bowel and an absence of haustral markings. A diagnosis was made of non-specific ulcerative colitis and the patient was treated with a bland, low residue diet, antispasmodics and rest. She made excellent progress during the next seventeen months and gained 13 pounds in weight. In May, 1935 the diarrhea recurred after the patient had taken Ex-lax for relief of constipation. She lost 8 pounds in two weeks. Proctoscopy revealed a granular, friable mucosa. Therapy was resumed but the patient was not seen again until January, 1945, eleven years after the initial examination.

She had enjoyed fairly good health until 1939, at which time the diarrhea had recurred and had persisted intermittently until July, 1943. Since that time the bowels apparently moved normally. The patient had been receiving injections of liver and iron and after one such treatment she experienced a sense of numbness at the site of injection on the exterior side of the right upper arm, followed by pain, redness and swelling of the area. A similar lesion soon appeared on the right leg. These became necrotic and ulcerated. Many boils subsequently appeared on the skin in various parts of the body; these lesions ulcerated and healed slowly, with residual scarring. The two original ulcerations, however, did not heal. In February, 1944 the patient was hospitalized elsewhere because of the ulcerations of the skin. Diagnoses were made of chronic ulcerative colitis and pyoderma gangrenosum. Therapy included twelve blood transfusions and 800,000 units of penicillin given intramuscularly; 20 per cent sulfathiazole in glucose was applied to the ulcerations. Definite improvement resulted although the lesions were not completely healed at the time the patient was discharged from the hospital.

In April, 1944 the patient sought relief at a second hospital because of the persistent and distressing cutaneous ulcerations. Hemolytic streptococci were isolated from cultures of the lesions. The lesions temporarily improved after each of four blood transfusions. Administration of 500,000 units of penicillin intramuscularly and 100 cc. of antistreptococcus serum intravenously, and 10 per cent sulfanilamide and 10 per cent sulfathiazole ointment applied locally were ineffective. The patient also received a high caloric diet, large amounts of vitamins A and C and such proprietary preparations as Ilextron

ferrous, aminoids and cortinoral. The local application of 10 per cent sulfanilamide and allantoin in a water-soluble base apparently exerted a beneficial effect temporarily. Skin grafting of the ulcerated areas was attempted in October, 1944 but these efforts were not successful. At the conclusion of this program of treatment the lesions on the right arm and right leg were not healed although definite improvement had occurred.

However, two months prior to the patient's admission to the Albert Merritt Billings Hospital in January, 1945 the ulcerations enlarged, bled easily, were painful and seriously interfered with movements of the right shoulder, elbow and leg. Pain in the back and both lower extremities at times was so marked as to require the use of codeine. Physical examination revealed an undernourished, chronically ill female. The significant findings were confined to the skin. Numerous fibrotic scars were present on the face, abdomen and inguinal regions and over both thighs. An enormous ulceration extended around the lower half of the right upper extremity and antecubital region; the base of the lesion consisted of poorly vascularized granulation tissue, partially covered with purulent exudate. Small red papules and pustules were located around the borders of the ulcerations. A similar gigantic lesion involved the lower half of the right leg. Smaller, more superficial ulcerations were present behind each ear. The erythrocyte count was 4.05 million, the hemoglobin 12.0 Gm. and the leukocyte count 9,800; the differential blood smear was normal. The Wassermann test was negative. Three urine specimens were normal. The plasma proteins measured 7.08 Gm. per cent. Six stool specimens were negative for *E. histolytica* and pathogenic bacteria. Detailed bacteriologic studies including aerobic and anaerobic cultures were made; *B. pyocyaneus* and *Staph. aureus* were isolated in several cultures. Careful repeated search for *E. histolytica*, various types of fungi and acid-fast organisms, including inoculation of the exudate into a guinea pig, were completely negative. A diagnosis of pyoderma gangrenosum was made. Various types of therapy were employed locally in an effort to stimulate healing of the cutaneous lesions. Five and 10 per cent ammoniated mercury and moist applications of penicillin in a concentration of 200 units per cc. were ineffective. Ultraviolet light was applied daily to the entire body and locally to each



FIG. 1. Case I. Extensive necrotizing pyoderma of the right upper extremity.

lesion. The patient's temperature remained moderately elevated, with peaks up to 38.5°C . A subcutaneous abscess, located over the right first rib, required surgical drainage. After six weeks wet dressings of silver nitrate solution, in a concentration of 1:10,000, were applied daily and 5 per cent silver nitrate was applied to the surfaces of the ulcerations after each change of a dressing. A distinct tendency to healing was observed several days after this therapy was instituted. Improvement continued but healing proceeded at an extremely slow rate. The patient also received vitamins, liver and iron and one transfusion of 600 cc. of whole blood. The lesions became less painful. The temperature gradually returned to normal and after two and one-half months of hospitalization the general condition of the patient improved sufficiently to enable her to continue treatment at home. It is of interest to note that no disturbance in bowel function occurred during this period; an average of one normal stool was passed daily.

Improvement of the cutaneous lesions was temporary, however, and the patient was readmitted to the hospital in April, 1945 because of an increase in the size and sensitivity of the ulcerations. These now involved the entire right arm from the shoulder to the elbow (Fig. 1) and the right leg from just below the knee to the ankle. (Fig. 2.) The base consisted in part of granulation tissue and in part of black necrotic masses covered with foul smelling, green purulent exudate. (Figs. 3 and 4.) Routine laboratory studies again were negative except



FIG. 2. Case I. Lesions involving the right leg with extensive ulcerations and purulent exudate.

for a mild secondary anemia. Therapy, with ultraviolet light and local applications of silver nitrate, 1:10,000 sol, was resumed. The lesions improved slowly but definitely. After three weeks of treatment the condition of the patient was considered to be better than at any previous stage of her illness. At this time she became much disturbed by a difficult family situation and was obliged to leave the hospital against advice. She has not returned subsequently for follow-up examination.

CASE II. R. C., No. 312075, a thirty-one year old male was first admitted to the Albert Meritt Billings Hospital in June, 1943. Three months before admission he had been ill with a pharyngitis which subsided after several days. Subsequently, the left shoulder, both knees and the right ankle became painful and swollen. Approximately three weeks before admission the patient developed lower abdominal cramping, pain and diarrhea; five to six semiformal, liquid stools containing bright red blood and mucus were passed daily. Additional symptoms included anorexia, a loss of 40 pounds in weight and marked weakness. Physical examination disclosed a markedly undernourished male. The skin was clear but very dry. The heart and lungs were normal. There was marked tenderness over the course of the colon. All joints appeared normal grossly; there was no visible edema of the extremities. The erythrocyte count measured 3.88 million and the hemoglobin 12.5 Gm. The leukocyte count was 19,350; 82 per cent of the cells were of the polymorphonuclear series. The value for total plasma proteins was 4.85 Gm. per cent; the albumin measured 3.24 Gm. and the globulin 1.61 Gm. Numerous examinations of the stools were



FIG. 3. Case 1. Biopsy from the edge of ulcer showing hyperkeratosis and benign hyperplasia of the epidermis. There is dilatation of the numerous blood vessels and the collagenic tissue is markedly edematous. $\times 125$.



FIG. 4. Case 1. Biopsy from the base of the ulcer showing infiltrate of polymorphonuclears, plasma cells, lymphocytes and connective tissue cells. $\times 130$.

negative for *E. histolytica*, other parasites and pathogenic organisms. Agglutination tests with the patient's serum against typhoid, salmonella and dysentery organisms were negative. Proctoscopy revealed a friable, edematous, bleeding mucosa, typical of the acute stage of non-specific ulcerative colitis.

The patient was treated medically for a period of 212 days. Therapy included the use of a bland, low residue diet, sedatives, anti-spasmodics and large amounts of vitamins. Sulfadiazine was administered in doses of 4.0 Gm. daily for periods of seventeen, five and eleven days. Sulfathalidine was given in doses of 12.0 Gm. daily for twenty days. Subsequently, sulfadiazine was resumed in quantities of 12.0 Gm. daily for eight days and then 4.0 Gm. daily for nine days. The patient received twenty transfusions of 600 cc. of whole blood, eight infusions of 500 cc. of plasma, large quantities of $2\frac{1}{2}$ per cent amigen in 10 per cent glucose solution and 10 per cent amigen in isotonic saline solution, 5 per cent glucose in saline as well as 10 per cent glucose in distilled water. No significant improvement occurred during this period of intensive therapy. The temperature remained almost constantly elevated, with sharp rises to levels of 39 and 40°C. As many as eighteen liquid stools containing blood and mucus were passed daily. A severe ulceration developed about the anal sphincter, with extensive sinus formation and the drainage of thick, mucopurulent exudate. On the 209th hospital day the patient passed per rectum approximately 150 cc. of blood together with liquid feces and purulent exudate. There was

continued slight loss of weight and persistent, moderately severe secondary anemia. The total plasma protein varied at first from 4.78 to 5.17 Gm. per cent; after administration of blood, plasma and amigen the values ranged from 5.34 to 6.32 Gm. per cent.

On the eighty-ninth hospital day several nodular lesions appeared on the nape of the neck. (Fig. 5.) Similar lesions developed almost simultaneously on the forehead, chest and back. The lesions represented acute inflammatory infiltrates with pustule formation in the pointed center and an acute erythematous border. The differential diagnosis included nodular toxic eruption, atypical erythema multiforme or septicemic emboli. Blood culture was negative. Bacteriologic study of the purulent exudate showed no bacteria. Microscopic examination of a biopsy specimen of one of the lesions was inconclusive. After several weeks the eruption gradually subsided but, three months later, similar lesions again developed on the nape of the neck. The character of the eruption now was less infiltrated and partly herpetiform, with groups of vesicles on an erythematous base. Several weeks later a confluent erythematous papular eruption was noted on the postero-lateral aspects of the neck, suggestive of toxic dermatitis. This gradually subsided without therapy.

An ileostomy was performed on the 213th hospital day. The patient's postoperative recovery was excellent. The temperature rapidly returned to normal. The patient gained 25 pounds in weight and he was discharged from the hospital forty-four days after operation. Improvement continued but five to six bloody



FIG. 5. Case II. Nodular and papulopustular lesions on the neck.



FIG. 6. Case II. Pyoderma left forearm. Note the many scars of previous lesions on the left arm and the neck.

discharges were passed from the rectum daily. The patient was readmitted to the hospital in April, 1945. Approximately one month earlier, furuncles had reappeared in various parts of the body. For one week the patient had experienced pain in both lower extremities. Physical examination revealed a fairly well nourished male who did not appear ill. There were many solitary reddened nodules, some of them displaying a purulent center, on the neck, arms, trunk, hips and left leg. (Figs. 6 and 7.) The ileostomy was functioning normally. Laboratory studies indicated moderately severe secondary anemia; the leukocyte counts varied from 11,000 to 16,450. Total plasma proteins ranged from 5.9 to 6.76 Gm. per cent. Proctoscopy disclosed a markedly inflamed friable, bleeding mucosa, covered with a bloody, mucopurulent exudate. The patient was treated with sedatives, feosol and sulfadiazine. Nine transfusions of 600 cc. of whole blood, 500 cc. of plasma, large amounts of amigen and isotonic saline solutions were administered. A total of 9,860,000 units of penicillin were given intramuscularly from the twelfth to the seventy-third hospital days. Two days after penicillin therapy was instituted the pyogenic lesions increased in number and severity. The eruption now consisted of follicular pustules and perifollicular infiltrates; a marked tendency to necrosis was noted in the larger lesions. The lesions closely resembled those present during the previous hospitalization period. A diagnosis of pyoderma gangrenosum was made at this stage. Cultures of the purulent exudate revealed hemolytic *Staph. aureus* and *B. pyocyaneus*. Therapy consisted of warm, moist applications of potassium permanganate

in a concentration of 1:8000 for five to fifteen minutes twice daily and the local application of 20 per cent ammoniated mercury ointment. Many of the lesions improved after three weeks of treatment. Colectomy was performed on the fifty-eighth hospital day. The entire bowel was shrunk and injected. Large lymph nodes were present in the thickened mesocolon. Gross and microscopic examinations of the bowel revealed the usual features of chronic non-specific ulcerative colitis. Recovery was uneventful and the patient was discharged seventeen days after operation. His subsequent course was remarkably good. Two and one-half months after colectomy the patient weighed 170 pounds, a gain in weight of 80 pounds since the initial hospitalization in 1943. All skin lesions had healed completely. His health remained good until January, 1948; intestinal obstruction with gangrene of the bowel developed at this time and progressed to fatal termination despite surgical intervention.

CASE III. D. O'D., No. 152942, a thirty-seven year old female school teacher, was first hospitalized in June, 1940. Approximately five years previously she had become ill with alternating diarrhea and constipation, generalized abdominal pain, loss of weight and fatigue. In April, 1936 blood and mucus appeared in the stools. A diagnosis of chronic non-specific ulcerative colitis was made and the patient responded to therapy emphasizing bed rest. Her subsequent course was characterized by frequent recurrences related to nervous tension, exertion and work. Improvement usually resulted when the patient stopped teaching and obtained adequate rest.



FIG. 7. Case II. A higher magnification of lesions shown in Figure 6. Some of them have herpetiform features (grouped vesicles).

Physical examination revealed a slender, pale young woman. The skin appeared normal. There was a swelling in the right tonsillar fossa with necrosis and ulceration. The erythrocyte count was 2.54 million, the hemoglobin 8.0 Gm. and the leukocyte count 12,000. The Wassermann and Kahn tests were negative. The stools were negative for parasites and pathogenic bacteria. Proctoscopic examination previously had revealed the typical features of non-specific ulcerative colitis. The patient received a transfusion of 450 cc. of whole blood and after spontaneous drainage of the peritonsillar abscess she was discharged from the hospital.

She was hospitalized again in January, 1941. Bloody diarrhea had recurred one month earlier. One week before admission she experienced loss of appetite and generalized muscular aching. At the same time several red and tender papules appeared on the back along the thoracic spine. These became pustular and similar lesions soon developed over the trunk and extremities. The temperature rose to 102°F. and a presumptive diagnosis of chickenpox was made. However, the patient had had the usual exanthemas, including chickenpox, during childhood. Physical examination revealed a poorly nourished female who appeared distressed but not acutely ill. Reddened, tender variably sized papules and occasional large pustules were present over the entire body. Some of the lesions were ulcerated and the bases of the ulcers were purulent. The diagnosis of pyoderma gangrenosum was made. The erythrocyte counts ranged from 3.58 million to 3.88 million; the hemoglobin 8.8 to 11.0 Gm. and the leukocyte count at first varied from 10,200 to 20,000; the white count later returned to normal. Many stools were negative for parasites and pathogenic bacteria but contained occult blood. The plasma



FIG. 8. Case III. Hypertrophic and atrophic, hyperpigmented and depigmented scars of the skin over the back in a patient with chronic non-specific ulcerative colitis and healed pyoderma gangrenosum.

proteins on two occasions measured 5.38 and 5.45 Gm. per cent; the albumin was 2.59 and the globulin 2.79 on one determination. Three blood cultures yielded no growth. Two cultures of the purulent material from the skin lesions were negative. X-rays of the chest revealed normal lung fields and the presence of cervical ribs.

The colitis was treated by bed rest, use of a bland diet, bismuth subnitrate and vitamins. Sulfanilamide, in amounts of 5.6 Gm. daily, was given from the twenty-ninth to the thirty-eighth hospital days. The skin lesions were treated by the daily general application of ultraviolet irradiation and local application of tincture of gentian violet. Improvement occurred slowly but gradually. The ulcerations on the neck proved more resistant to therapy and drained purulent exudate for several weeks. Marked improvement was noted on the seventieth day. Many of the ulcerations had healed with residual atrophic scarring. At the end of three months all skin lesions had healed and the patient was discharged from the hospital.

In July, 1945 the patient suffered a recurrence of the ulcerative colitis and she lost 15 pounds in

weight. At this time also there was a recurrence of the cutaneous lesions, involving especially the back and both legs. The patient was hospitalized elsewhere and gradually recovered. The skin lesions slowly healed, with production of thin, atrophic scars.

The patient was last seen in July, 1946 at which time she appeared to be under considerable emotional tension. Two or three moderately formed stools without gross blood were passed daily. There were no ulcerations of the skin but many atrophic scars of former lesions were present. Figure 8 demonstrates the end stages of pyoderma gangrenosum in this case.

COMMENT

Pyoderma gangrenosum may be a serious complication of chronic non-specific ulcerative colitis and, as illustrated by Case I, may assume greater clinical significance than the primary disease. Chronicity of the lesions and resultant disability of the patient tax the ingenuity and patience of the most resourceful physician. It is apparent from these case studies that the bacterial flora of these pustular and ulcerative lesions is not uniform and not pathognomonic and that some of the purulent lesions may even be sterile. Correspondingly, large quantities of sulfonamides and penicillin have little value either prophylactically or therapeutically. Obviously decreased resistance of the skin organ and its great tendency to tissue necrosis is a more important factor in the pathogenesis of pyoderma gangrenosum than is bacterial infection. The decrease in resistance, however, does not depend solely on the severity of the colon infection or on the subsequent state of malnutrition. Pyoderma gangrenosum developed in the first patient when the ulcerative colitis was in a quiescent state and it recurred in the second patient despite a satisfactory clinical response to ileostomy. Yet, the further course in Case II indicates that there must be a direct connection between primary bowel disease and skin manifestations for after the infected colon was resected the pyoderma subsided completely and permanently. At the present time it seems that control of the underlying chronic disease and restoration of a normal state of nutrition are the best

methods for prevention and successful treatment of pyoderma gangrenosum.

SUMMARY

Three cases of pyoderma gangrenosum complicating chronic non-specific ulcerative colitis are described in detail. No pathognomonic flora was found and some of the purulent lesions were sterile. Large quantities of sulfonamides and penicillin were of no value either prophylactically or therapeutically. Improvement in Case I followed improvement of the general condition of the patient and persistent local therapy with ultraviolet light and silver nitrate solutions. Complete recovery in Case II was achieved after resection of the infected colon and restoration of a normal state of nutrition. The third patient recovered after use of ultraviolet light therapy, local application of tincture of gentian violet and control of the chronic non-specific ulcerative colitis.

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Unusual Strain of *Pseudomonas Aeruginosa* Recovered from the Urinary Bladder

Effects of Streptomycin

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PSEUDOMONAS aeruginosa (*B. pyocyaneus*) which was first isolated by Gessard⁵ in 1872, has been recognized for years as the organism which produces "blue pus" and much speculation has arisen concerning its rôle as a primary invader and the degree of pathogenicity it shows in human beings. Since 1890, there have been divergent views concerning the rôle this organism plays in disease. Marthen⁹ (1890), in an essay discussed the implications of the "blue pus organism" and emphasized the occurrence of paralysis in patients and laboratory animals infected with virulent strains of *B. pyocyaneus*. He noted that the bacteria-free filtrate contained: (1) The greenish pigment "pyocyanine" and (2) an exotoxin which produced various effects including albuminuria and paralysis of varying degree when injected into laboratory animals. He also stated that immunization could be attained by inoculating animals with sub-lethal doses of bacteria.

In proof of the virulence that may be displayed by *B. pyocyaneus* in infections, Edel³ collected several case histories in which fatalities were described. Bernhardt¹ and Klieneberger⁶ reported cystitis and nephritis which were directly attributable to the organism. Loder⁸ found that experimental animals frequently succumbed within six to twelve hours after inoculation, showing a severe terminal drop of body temperature. General infections with *Ps. aeruginosa*,

while of rare occurrence in healthy adults, are more common in children and debilitated adults. (Musser and Sodeman.)¹⁰ These investigators maintained that paralysis of smooth muscle and paresis of the leg musculature with subsequent atrophic changes may follow absorption of the pyocyanous toxin. Clawson and Young² isolated hydrocyanic acid from the exotoxin produced in broth cultures of *Ps. aeruginosa* but to a less extent from *in vivo* examinations.

Although considerable literature has accumulated on the bacteriological and to a less extent on the clinical aspects of the *Ps. aeruginosa*, little work has been done in differentiating various strains of bacilli constituting this group. Although bacteriologists have often discussed the question of bacterial variability or mutation, they have rarely referred to examples of urinary tract infections with atypical organisms. This is not solely an academic problem, because it is possible that in a changed form a bacterium may play an entirely different rôle than the parent strain.

It is known for example that the relative degree of virulence of certain bacteria can be roughly estimated by the character of the colonies they produce on agar plates. Those in the so-called "S" or smooth category are believed to exhibit increased virulence. The second group, known as the "R" or rough group, (because of the irregular contours which the colonies show on agar

plates) contains organisms which show less virulence. The third category, of which only slight mention has been made in medical literature, is known as the "M" or mucoid group because of the characteristic mucoid appearance of the colonies. Bacteria in this category frequently have distinct capsules and show higher grades of virulence. Organisms belonging to the three groups may be present singly or in association. In this paper we propose to deal with the mucoid variant of *Ps. aeruginosa*.

CASE REPORTS

CASE I. Mr. J. P. was operated on by the senior author March 13, 1946. A right nephrectomy and subtotal ureterectomy was performed for suppurative pyelonephritis, ureteritis and multiple renal calculi. During the course of a routine follow-up urological examination on April 9, 1946, gram-negative encapsulated rods were recovered from the bladder urine. Urine from the left kidney was negative on smear and sterile on culture. Colonies on blood agar plates were distinctive because of mucoid, massed appearance and a striking hemolytic tendency.

The organism, a blunt rod occurring singly, in pairs and in short chains, presented well defined capsules on an ordinary Gram stain. On Leifson's modification of the flagella stain, three flagella were noted, two at one pole and one at the other. After secondary cultivation, however, the capsules could be seen only when treated with regular capsule stains. The organism fermented dextrose but merely produced an insignificant amount of acid. In view of the close similarity to Friedländer bacillus and *Aerobacter aerogenes*, it was deemed advisable to carry out further studies before the specific identity of the organism could be established. Following inoculation of routine differential media the organism was found to be a mucoid variant of *Ps. aeruginosa*. Owing to close resemblance to *Pseudomonas fluorescens*, differentiation could be made only by establishing its pathogenicity by means of animal inoculations. *In vivo* studies readily disclosed that we were dealing with a virulent bacterium of great

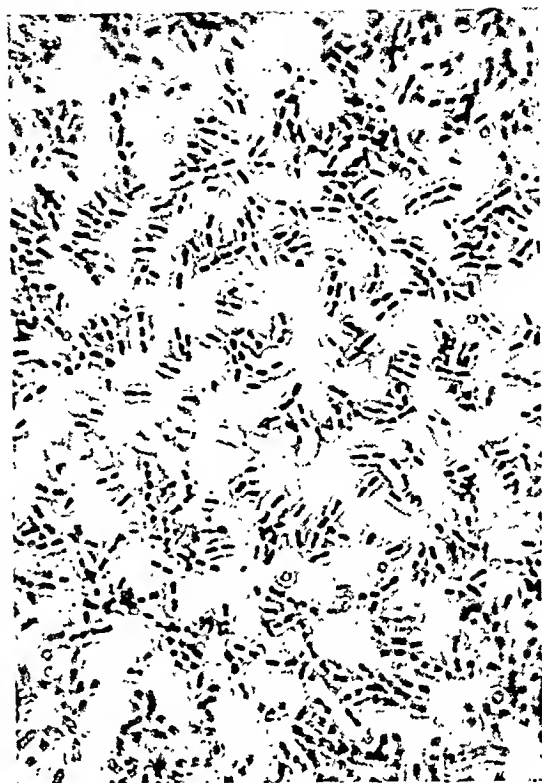


FIG. 1. Mucoid variant of *B. pyocyaneus* on primary isolation showing capsule. $\times 1250$.

toxicity which in doses as low as $\frac{1}{10}$ ml. proved rapidly fatal to mice weighing 20 Gm. Before death all inoculated mice showed evidence of hind limb paralysis.

Smears of the centrifuged urine showed many Gram-negative rods measuring approximately 0.5 to 0.6 by 1.5 microns. Blood agar plates were streaked and broth tubes inoculated with the sediment. After twenty-four hours luxuriant growth was noted on the plates and in the tubes. The colonies were grayish, presented smooth borders and were beginning to assume a massed appearance. When touched with the inoculating needle, they were found to be extremely mucoid as shown by their tendency to follow the needle in long strings. Microscopically the organism appeared as a gram-negative rod with a well defined capsule. (Fig. 1.) It was motile and produced no acid or gas on Kligler's iron agar, thus differentiating it from the *Klebsiella pneumoniae* and *Aerobacter aerogenes*. Broth cultures contained a green pigment which was soluble in water and chloroform. Nitrates were reduced and litmus milk rapidly peptonized with production of alkali. Gelatin and Loeffler's



FIG. 2. Colonies of *K. pneumoniae* on tryptose phosphate agar.

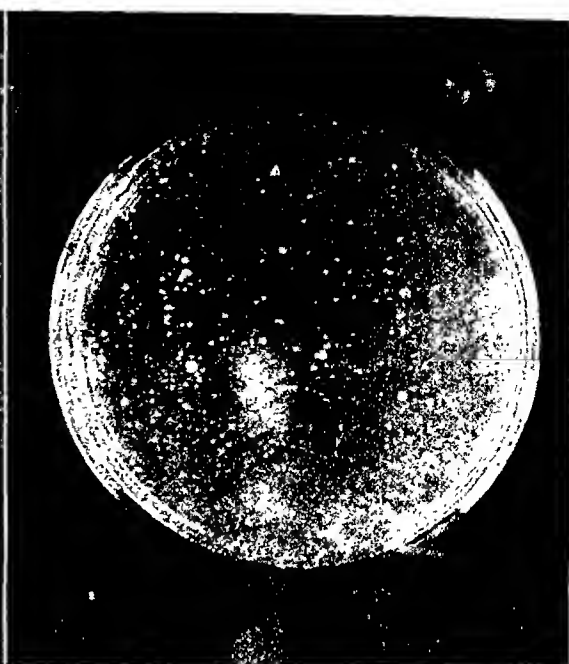


FIG. 3. Colonies of *B. pyocyaneus* on tryptose phosphate agar.

serum were promptly liquefied and the blood hemolyzed.

DIFFERENTIATION FROM *KLEBSIELLA PNEUMONIAE* (FRIEDLÄNDER BACILLUS)

Klebsiella pneumoniae, which occasionally is isolated from the urine, closely simulates the mucoid variant of *Ps. aeruginosa*, especially in regard to the appearance of its colonies on blood agar plates. (Figs. 2 to 5.)

This organism (first described by Friedländer⁷ in 1882), is a gram-negative rod measuring approximately 0.3 to 0.5 by 5.0 microns. It is found alone and in pairs; it is encapsulated but shows no motility. It ferments dextrose, sucrose, lactose, levulose and galactose with the formation of acid and gas. It may ferment maltose but not mannitol. Sugar fermentations are unreliable, however, and serological typing should be done for correct identification. Nitrates are reduced to nitrites, litmus milk is acidified but gelatin is not liquefied. Colonies on blood agar plates are large, grayish in color and present smooth or rough borders and a

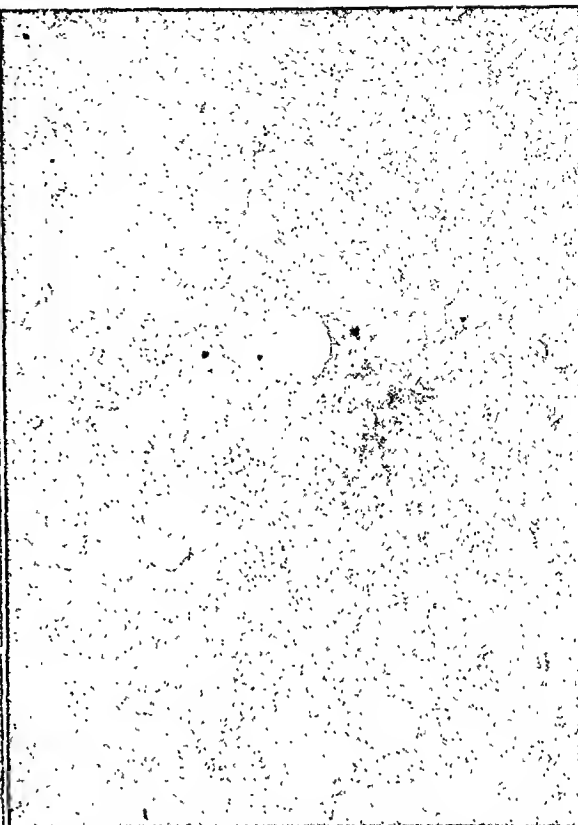
massed appearance. The blood is not hemolyzed.

DIFFERENTIATION FROM *AEROBACTER AEROGENES*

Aerobacter aerogenes (discovered by Kruse⁷ in 1896), is a gram-negative rod measuring approximately 0.5 to 0.8 by 1.0 to 2.0 microns and appears singly. It may be motile or non-motile and is frequently encapsulated. Dextrose, lactose, maltose, levulose and galactose are fermented with the production of acid and gas. Sucrose may be fermented and nitrates are reduced to nitrites. The blood is not hemolyzed, gelatin is not liquefied but litmus milk is acidified. On blood agar plates the colonies are large, appear grayish, are of a mucoid, heaped appearance and may present smooth or rough borders.

LABORATORY PROCEDURE

Errors in diagnosis are inevitable in view of the occasional tendency to identify organisms by the appearance of their colonies on blood agar plates. To avoid these errors when dealing with colonies

FIG. 4. Colonies of *K. pneumoniae*. $\times 500$.FIG. 5. Colonies of smooth mucoid variant of *B. pyocyaneus*. $\times 500$.

similar to those previously described we have established the following routine. A single colony is examined for purity by the Gram stain. A pure culture of the gram-negative rod is then planted on Kligler's iron agar. Care must be taken, not only to stab the butt of the slant, but also to streak the surface of the agar. After twenty-four hours the agar is examined and a tube of broth media is inoculated in order to demonstrate motility. If the slant appears unchanged and a strong odor is present and if the broth tube discloses a motile rod, it may be presumed that the organism is one belonging to the group of *Ps. aeruginosa*. If the agar tube is of a uniform yellow (with bubbles) and if acid and gas are present, inoculations are promptly made into dextrose, lactose, sucrose, maltose, mannitol, nitrate media and litmus milk. Clark and Lubbs's media is used for the determination of methyl red and Voges-Proskauer's correlation is used if the organ-

ism ferments maltose in order to differentiate it from *E. coli*. If maltose does not ferment and the remainder of the tests prove positive, it may be presumed that the organism is *K. pneumoniae*. If maltose is fermented, all the other tests (including Voges-Proskauer) prove positive, the methyl red test negative and the organisms are *not* agglutinated by pneumoniae antiserum the organism may be identified as *A. aerogenes*. If the methyl red test is positive and a Voges-Proskauer test negative, the organism is *E. coli*.

IN VIVO EXPERIMENTS WITH STREPTOMYCIN

Two rabbits were inoculated intravenously with 3 cc. of suspension of organisms washed with sterile saline. Rabbit No. 1 received 10,000 micrograms of streptomycin three hours after inoculation and a similar dose four hours later. The temperature rose from 102.2°F. to 104°F. six hours later. Within forty-eight hours after

inoculation, the animal began to show signs of paralysis of the hind limbs, the body temperature dropped to subnormal and bowel movements became loose and frequent. Death ensued a few hours later.

Postmortem examination was immediately performed and revealed: (1) Bilateral hemothorax with approximately 15 cc. of sanguineous, frothy fluid in each pleural sac as well as multiple abscesses in both lungs. A pure growth of *B. pyocyaneus* was recovered on smear and culture; (2) the heart muscle showed a few miliary abscesses and *B. pyocyaneus* was found in the heart's blood; (3) miliary abscesses were also seen in the liver and kidneys. The central nervous system was not examined.

Rabbit No. 2 was eight months old and weighed 3 pounds; it was inoculated intravenously with 3 cc. of a broth culture. Before inoculation the rabbit's temperature was 101.8°F. Twenty-four hours later the rabbit received 20,000 micrograms of streptomycin intravenously; the temperature then dropped to 100°F.; the animal appeared acutely ill and refused food. In five days, however, it had completely recovered except for a necrotic area at the site of the original inoculation. There were no sequelae. The rabbit was again inoculated with 4.5 cc. of a broth culture, and the only reaction noted was an erythema at the site of inoculation. Although under careful surveillance for three weeks no ill effects were noted.

Using the same encapsulated organism which had been transplanted weekly on Bacto tryptose broth media for two months, 5 cc. of a month old growth was injected intraperitoneally into a female albino guinea pig. The animal succumbed in thirty-six hours. At postmortem examination multiple small abscesses were discovered in the left lung, kidneys and adrenals. The stomach, liver and intestine were covered with a malodorous, bluish-white mucopurulent exudate. The liver and spleen showed chronic passive congestion and inflammatory changes. The urinary bladder was also covered with a fibropurulent exudate. The spinal cord was apparently uninvolved but the subarachnoid space over the brain was filled with mucopurulent exudate. The brain, however, disclosed no pathological changes. Smears taken from the

affected organs showed many macrophages and gram-negative encapsulated rods (*Ps. aeruginosa*).

In order to ascertain the toxic source the following experiments were carried out:

(1) A ninety-six-hour tryptose broth culture of *B. pyocyaneus* (mucoid variety) was filtered through a Seitz filter. The pigment was extracted by repeated washings with chloroform. The pure pigment was then evaporated to dryness. This crystalline substance was dissolved in 5 cc. of distilled water and sterilized in the autoclave under 15 pounds of pressure for fifteen minutes. The solution was then inoculated intraperitoneally into a female albino pig. Careful observation of the animal for seven days disclosed that it suffered no ill effects, thereby proving that the pigment pyocyanine was innocuous. (2) Following the intraperitoneal injection of 8 cc. of toxin filtrate into a guinea pig the animal had a convulsive seizure which lasted for twenty-five minutes. After one hour it was semicomatose and showed signs of paralysis of the hind limbs. Complete recovery occurred in seventy-two hours. (3) An albino pig received 5 cc. of a four-week old tryptose broth culture of *B. pyocyaneus* which was a daughter strain of the original mucoid colony isolated two months previously. Five minutes after the injection the animal developed urinary incontinence, incomplete hind limb paralysis and loss of equilibrium. It lost all interest in food. Ten minutes after the inoculation it was semicomatose and developed complete paralysis of the hind limbs making it impossible for it to remain upright. Respirations were very rapid. Death ensued forty-eight hours after inoculation.

These experiments indicated that (1) even old cultures of the mucoid variant of *Ps. aeruginosa* retain their high virulence; (2) the bacteria-free filtrates are not fatal to laboratory animals and (3) the pigment pyocyanine apparently plays no rôle in the pathogenicity of the organism. It appears, therefore, that the toxicity of this bacillus is probably due to an endotoxin which is capable of causing a multiplicity of visceral lesions.

On June 18, 1946, a third culture was made of the bladder urine of the patient which again disclosed the same organism. A 4 pound albino

female rabbit was inoculated with 4 cc. of a twenty-four-hour culture (washed suspension). The only result was to make the animal extremely lethargic. Two days later the animal received 25 cc. of a seventy-two-hour tryptose broth culture (organisms and toxin) intravenously. Within three minutes it became restless and after five minutes had two convulsive seizures and expired after the second convulsion.

Postmortem examination disclosed perihepatitis, multiple liver abscesses and hemorrhage in the left orbit. There was also a pronounced leptomeningitis hemorrhagica involving the meninges of the brain and cord with hemorrhages and purulent exudate within the substance of these structures. Smears from the liver showed thick encapsulated rods (*Ps. aeruginosa*) identical with those of the original culture.

Treatment of the patient with streptomycin was now begun. The initial dose (May 7, 1946), was 500,000 micrograms which was followed by a similar dose three hours later; then 100,000 micrograms were administered at three-hour intervals. A urine culture made after the second dose was sterile and remained so until June 7, 1946, when a pure culture of a "smooth" strain of *Ps. aeruginosa* was isolated. Careful study of this organism showed it to be non-encapsulated, amotile and much less virulent than the mucoid strain as was shown when it was injected intraperitoneally into a 4-pound male rabbit. The only result was the formation of an abscess at the site of inoculation. A urine culture (June 19, 1946), however, again revealed a pure culture of the mucoid strain, the organism disclosing characteristics which were identical with those of the original strain except that its virulence was notably diminished.

At this point we concluded that (1) streptomycin in a dosage of 5,000,000 micrograms had only a transient inhibitory effect on the organism; (2) one month after discontinuance of the antibiotic we recovered another strain (smooth) of *Ps. aeruginosa*; (3) twelve days later a culture of the bladder urine again showed the original strain (mucoid) but of a reduced virulence.

The question naturally arose as to whether or not we were dealing with an example of mutation of bacteria or with two different strains of the same group. In the former instance it would

be necessary to postulate that streptomycin was instrumental in causing (1) noteworthy but temporary bacteriostasis so that for one month after discontinuance of the drug repeated cultures were sterile; (2) a change in physical characteristics of the bacillus, in that the colonies lost their mucoid appearance and the organism its characteristic capsule; (3) a definite decrease in virulence and pathogenicity. In the last noted instance we must assume the simultaneous presence of both strains of organisms at the time of preparing the original culture, in which the predominant strain (namely, the mucoid variety) completely overgrew and masked the other (smooth) strain. Upon the administration of streptomycin there occurred an abrupt inhibition of both strains, more sustained, however, in the case of the mucoid variety with the result that on cultures taken one month after discontinuance of the antibiotic only the smooth species was recovered. A later culture, however, showed the mucoid organism again active and predominant but displaying decreased virulence.

On July 7, 1946, Mr. J. P. reported feeling well but complained of occasional increased urinary frequency. Urinalysis showed albumin 2+ and many leukocytes. Culture of the bladder urine again showed the smooth mucoid encapsulated variant of *Ps. aeruginosa*.

Two rabbits were inoculated, one intraperitoneally with 11 cc. of a ninety-six-hour washed suspension of *Ps. aeruginosa* containing toxin and pyocyanine and the other intravenously with 3 cc. of the same suspension. The first rabbit succumbed in twelve hours and the second five minutes after the inoculation.

Necropsy performed on rabbit No. 1 disclosed pneumonitis involving the left lung and miliary abscesses of the right lung. There was hemorrhagic infiltration of the wall of the large bowel, most pronounced in the cecum. The stomach showed a spontaneous laceration of its wall near the cardia, measuring approximately 3 cm., with a large amount of gastric contents present in the upper abdomen. There were several abscesses in the right lobe of the liver. The kidneys and adrenals were apparently unaffected. The spinal cord showed many hemorrhages. Gram-negative encapsulated rods

were found in smears taken from abscesses in the liver and lung.

In view of the highly pathogenic character of this organism in animal experiments and the few symptoms shown by the patient, we instilled 2.5 cc. of a ninety-six-hour broth culture into the bladder of a full-grown female rabbit through a ureteral catheter. After seventy-two hours the rabbit developed urinary frequency but no other symptoms. Specimens of urine showed many leukocytes and encapsulated rods (*Ps. aeruginosa*) in smears. Nine days later despite positive urinary data the animal was completely asymptomatic.

CASE 11. Mr. C. H. Y., forty-three years of age, was first seen on December 18, 1933, complaining of painful hematuria and increased diurnal and nocturnal urinary frequency of four days' duration. During the previous five years he had sustained attacks of right renal colic and for four and one-half years attacks of left renal colic. A complete urological examination disclosed a small calculus in the bladder, moderate hydronephrosis of the left pelvis, hypertension (174/80) and mitral stenosis. The vesical calculus was removed cystoscopically.

The patient was next seen in consultation on August 15, 1946. During the previous several weeks he had been under medical care for hypertension, his blood pressure varying between 230/140 and 170/80. A flat film of the kidneys disclosed a large stag-horn calculus in the pelvis of the left kidney. During the previous week his temperature ranged between 101°F. and 102°F. A complete urological examination elsewhere showed a well functioning kidney and normal pelvis on the right side. The left pelvis was moderately dilated especially the upper calyx. Treatment consisted of ureteral drainage of the left pelvis. During the consultation period the temperature was 103°F. and definite left costo-vertebral tenderness was elicited. Primary cultures from the left kidney were reported showing *Staphylococcus albus*. Subsequently, a pure growth of *E. coli* and finally *Ps. aeruginosa* (mucoid variant) were observed. Pre-surgical diagnosis: Left renal calculus and suppurative pyelonephritis (multiple abscesses).

Operation was performed August 16, 1946, by the senior author. Under spinal anesthesia

the left kidney was exposed through a 7 inch Albarran incision. The organ was moderately enlarged and presented considerable perinephritis. Upon stripping the capsule groups of miliary abscesses were found on the anterior surface of the kidney above the hilus and over both renal poles. There was a large, hard, stag-horn calculus in the renal pelvis. The calices were moderately dilated especially the superior one. In view of the presence of sufficient renal parenchyma it was deemed advisable to conserve the kidney. The calculus was removed through a nephrostomy opening and the pelvis drained with a soft rubber tube. The operation was concluded by draining the renal fossa and closing the wound in layers. A transfusion of 500 cc. of blood was given immediately following the operation.

During the postsurgical period the general condition of the patient was excellent despite failure of the temperature to subside. (101°F. to 102°F.) Drainage through the nephrostomy tube was scanty for the first forty-eight hours but finally increased to 100 to 200 cc. daily. Streptomycin was administered in doses which will be described at a later point. Approximately seven days after surgery the patient developed a persistent severe hematuria. Several transfusions were given and vitamin K administered but bleeding continued. In view of our inability to control the bleeding plus the continued fever, the persistence of positive cultures of *Ps. aeruginosa* (mucoid variant) and despite the administration of 13,000,000 micrograms of streptomycin, it was deemed advisable to remove the kidney.

The operation was performed on August 30, 1946. Under cyclopropane anesthesia the kidney was exposed by reopening the original wound. Profuse bleeding occurred as soon as the nephrostomy tube was removed. The kidney was enlarged, boggy and felt very warm to the touch. A moderate number of cortical abscesses could still be seen in the renal cortex but these were not as conspicuous as they were at the time of the previous operation. The renal pedicle and ureter were doubly ligated and the kidney quickly removed. The renal fossa was drained and the wound closed in layers. A transfusion

of 500 cc. of blood was administered at the conclusion of the operation.

The pathologist's report (Dr. A. Schifrin) was as follows: Macroscopic: "The specimen consists of a large kidney which has been stripped of its capsule. It measures $10 \times 7 \times 6.5$ cubic centimeters. No stones are present within the specimen received (the calculus, it will be remembered, was removed at previous operation). The pelvis had been opened and was moderately dilated. Several large friable and firmly adherent blood clots are present. At one pole adjacent to a dilated calyx there is a triangular, firm, partly whitened blood clot. The pelvic wall at this site is hemorrhagic and ulcerated. Other parts of the pelvis and some of the calices show hemorrhagic indurations and ulcerations of their wall. The renal parenchyma is broad and its markings are indistinct. They contain numerous white and hemorrhagic streaks. The renal surface (stripped of its capsule) shows numerous small and larger elevations and depressions, most of which correspond to the streaked whitish and hemorrhagic parenchyma noted above. The uretero-pelvic junction is not dilated.

"Microscopic: Kidney. Section through the pelvis and calices shows extensive ulceration of the mucosa with an overlying broad zone of clotted blood. The base of the ulceration is lined by granulation tissue containing numerous small blood vessels and showing interstitial hemorrhage and infiltration by numerous round cells, scattered polys and numerous plasma cells. Fibrosis is present. There are numerous foci of interstitial infiltration of the renal parenchyma by dense aggregation of round cells, plasma cells and polys. In some places these show small abscess formation with central hemorrhagic zones filled with polymorphonuclear leukocytes and necrobiotic nuclei. In places these foci are conglomerate. There is scattered interstitial fibrosis of the parenchyma with occasional foci containing dilated tubules with calcium encrusted epithelial cells. There are foci of fibrosis and renal atrophy beneath depressed areas of renal surface. The boss-like elevation of renal surface contains numerous microscopic abscesses within the subjacent parenchyma.

"Diagnosis: (1) Severe chronic and acute hemorrhagic ulcerative pyelitis and calicitis; (2) severe interstitial chronic and recurrent pyelonephritis with small abscess formations."

Following the nephrectomy the patient's temperature promptly subsided and he was discharged from the hospital after an uneventful convalescence, in excellent condition on September 11, 1946.

URINARY CULTURE STUDIES IN RELATION TO STREPTOMYCIN

A rabbit inoculated intravenously with 5 cc. of a washed suspension of the primary culture (August 17, 1946), expired in seven hours and was promptly autopsied. The examination showed extensive blood clots in the nose, mouth, rectum and urethra. Blood was present in the peritoneal, pleural and pericardial cavities. A small rupture was noted in the bladder in the region of the right ureter. Multiple abscesses were present in the kidneys, adrenals, gastric wall, pancreas, lungs, omentum and liver. Evidence of a previous massive hemorrhage was found in the brain. *Ps. aeruginosa* (encapsulated) was recovered on smear and culture from the various affected organs.

Streptomycin therapy was instituted on August 19, 1946. Ten doses of 500,000 micrograms each were administered at three-hour intervals, followed by forty-eight doses of 125,000 micrograms each and 5 doses of 400,000 micrograms each, using the same three-hour interval between doses. The total was 13,000,000 micrograms.

Cultures, which were taken every twelve hours, remained positive until September 8, 1946, when the first negative culture was obtained. In order to ascertain the virulence of the organism, several rabbits were inoculated intravenously with 5 cc. of washed-cell suspensions taken from the various cultures. The first four cultures showed intense virulence, the rabbits succumbing in seven to twelve hours. After 2,000,000 micrograms were administered, the colonies

changed to the rough variety and retained this characteristic throughout the remainder of the treatment until two negative cultures were obtained. However, a culture taken on September 11, 1946, again showed rough colonies (non-encapsulated).

Eight rabbits were inoculated with an organism taken from the rough colonies and of these two expired and one was sacrificed. Two rabbits showed paralysis of all their limbs which lasted for approximately five days and was followed by full recovery. Postmortem examination of the two rabbits and of the sacrificed animal showed minimal changes except for diffuse hyperemia of the viscera. A few rabbits presented abscesses at the site of inoculation.

CASE III. Mr. L. H. W., seventy-three years of age, was first seen on May 24, 1945, complaining of painless hematuria of five months' duration. A urological examination disclosed two large solid tumors situated on the posterior wall of the bladder near the vault. The prostate was enlarged.

An extensive segmental resection of the bladder was carried out on May 30, 1945, by the senior author and was followed-up with a full course of deep roentgen therapy. A transurethral resection was performed June 20, 1946. On September 1, 1946, the patient developed fulminating urosepsis with a positive blood culture of gram-negative rod (*Ps. aeruginosa*) appearing on September 12, 1946.

Sub-surface colonies showed extensive greening while the surface colonies appeared smooth and glistening. Transplants were made on gelatin, Loeffler's blood serum, Russell's double sugar agar medium and on the sugars maltose, sucrose, dextrose and lactose. Only fermentation of dextrose occurred but no gas was formed. The blood serum showed a mutation of the organism to the mucoid phase with extensive greening of the media and extremely slow liquefaction. The odor of trimethylamine usually associated with pyocyanus was absent. Proteolysis was not as pronounced as in any of the previous organisms studied. Proteins were split only to ammonia and the nitrates reduced solely to

nitrites. There was no tendency to hemolyze blood. Pyocyanine was present in small amounts, the prominent dye product being fluorescein. This was shown by the fact that the dye was soluble in water with which it could be extracted from cultures.

A five-month old, white, male rabbit was inoculated intravenously at 11:00 A.M., September 17, 1946, with 5 cc. of a twenty-four-hour broth culture of the mucoid strain of the organism. The animal exhibited neurological symptoms within three hours, such as pronounced head tremor and hind limb paralysis. One hour before death the body temperature dropped from 101.6°F. (normal) to 98°F. Death occurred six hours and forty-five minutes after inoculation and was preceded by vomiting, diarrhea and severe convulsive seizures.

On opening the abdomen an odor of trimethylamine was distinctly noticeable and the undersurface of the abdominal integument presented a greenish fluorescent hue. The spleen was enlarged and congested while the liver showed several small punctate abscesses. The lungs appeared congested and a small abscess was present in the left lower lobe. The meninges over the brain showed multiple hemorrhages and a moderate amount of mucopurulent exudate. Three large abscesses were present on the undersurface of the brain. The spinal cord appeared hyperemic. Smears of all lesions showed gram-negative bacilli (non-encapsulated).

Treatment of the patient was started September 13, 1946, with 500,000 micrograms of streptomycin hydrochloride.* This dose was repeated at three-hour intervals for a total of 20,000,000 micrograms. The first negative culture was obtained at 4:00 P.M., September 15, 1946, after the administration of 7,500,000 micrograms. A second negative culture was obtained at 2:00 P.M. September 16, 1946. Although prior to the use of the antibiotic the patient was virtually moribund, within forty-eight hours after the administration of the first dose of streptomycin he was fully alert and his temperature dropped from 104°F. to normal. At the completion of streptomycin therapy all traces of sepsis had disappeared.

* A Merck product.

SUMMARY AND CONCLUSIONS

During a routine urological follow-up examination of a patient previously nephrectomized for calculous pyelonephritis, an unusual organism was recovered from the bladder urine, which was a mucoid variant of *Ps. aeruginosa*. The organism formed characteristic colonies on blood agar plates and disclosed microscopically well defined capsules. There was a very close similarity of the organism to Friedländer bacillus and *Aerobacter aerogenes*. When injected intravenously and intraperitoneally into laboratory animals, it proved to be highly virulent. However, when a suspension of the bacilli was instilled into the bladder of a rabbit it produced only a mild cystitis. Streptomycin in doses totalling 5,000,000 micrograms, although causing a noteworthy bacteriostatic effect, failed to destroy the organism. Shortly after the administration of the antibiotic, the bacterium temporarily lost its capsule and the colonies showed a distinct change in their mucoid appearance. A concomitant drop in virulence also occurred. Subsequent cultures, however, disclosed the reappearance of encapsulated rods, a return of the mucoid appearance of the colonies on agar plates and a striking increase in virulence.

An identical organism was recovered from the urine of a patient suffering from calculus and suppurative pyelonephritis involving the left kidney. Following a nephrolithotomy, decapsulation and drainage of the kidney 13,000,000 micrograms of streptomycin was administered. After 2,000,000 micrograms were given the rods lost their capsules and virulence diminished. At the conclusion of the full course of treatment, two negative cultures were obtained; a third culture, however, again showed *Ps. aeruginosa* (non-encapsulated). Owing to persistent, severe hematuria, failure of the fever to subside and despite the adminis-

tration of 13,000,000 micrograms of streptomycin it became necessary to remove the kidney. Examination of the extirpated kidney still showed the presence of multiple abscesses. Following nephrectomy all symptoms disappeared even though organisms were still recoverable on culture from the bladder urine.

Ps. aeruginosa was also recovered from a patient with urosepsis following segmental resection of the bladder for extensive carcinoma. Blood serum from this patient showed mutation of the organism to the mucoid phase. Following the administration of 20,000,000 micrograms of streptomycin in doses of 500,000 micrograms every three hours, a complete recovery occurred despite the fact that the patient was moribund at the time treatment was instituted. In this instance the first negative blood culture was obtained after he had received 7,500,000 micrograms of streptomycin.

We believe that despite the paucity of symptoms among some patients harboring *Ps. aeruginosa* in the urinary tract, the organism, especially the mucoid variant, possesses a noteworthy virulence and pathogenic propensity. Although resistant to all urinary antiseptics, including streptomycin in doses recommended by the Division of Medical Science, National Research Council, it is possible that massive doses may prove bactericidal. Careful bacteriological examinations are not only necessary to establish the true identity of the various strains of bacilli belonging to this category but in the determination of effective therapy as well.

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875 Park Ave.

What Value Enteric Coating^{*}

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MANY drugs tend to upset the stomach. They will, in some instances, cause nausea, heart-burn, bloating, pain in the epigastrium, cramps and even vomiting. In order to avoid such local effects of the drug on the gastric mucosa they are often administered in the form of enteric-coated tablets. Enteric coatings of one kind or another have been in use since 1884 when Unna used keratin for this purpose.

The composition of the coatings differs. One widely used formula consists of a "powdered mixture of fatty acid, wax and hygroscopic vegetable components, with white shellac as a binding agent."¹ Pharmaceutical houses vary their formulas.

We do not propose to discuss at this time the advisability of enteric-coated drugs. The question for the present is whether or not the enteric coating always accomplishes the desired effect.

Noting a striking lack of uniformity in the therapeutic effects of two well known brands of enteric-coated ammonium chloride tablets, we proceeded to investigate the possible reasons therefor. We were rather surprised to learn that one of the preparations distributed by a reputable drug company failed to have any effect in four of five cases as judged by its use in congestive cardiac failure in conjunction with mercurial diuretics. The reason for its inefficacy became obvious when we found that in four cases out of five the tablets not only failed to disintegrate in the stomach but passed through the entire digestive tract practically unchanged. (Fig. 1.) Yet the label on this preparation read: "The special enteric coating protects the tablet from gastric secretions. It will disintegrate in the duodenum."

At the other extreme another brand of enteric-coated ammonium chloride tablets disintegrated in the stomach thus defeating



FIG. 1. Roentgenogram showing shadows of the tablets in the colon which were not disintegrated.

the purpose of the coating. Disintegration of this brand within one hour of its ingestion is demonstrated in Figure 2. In addition, ammonium chloride was demonstrated chemically in the gastric contents.

After procuring descriptions of the methods used by pharmaceutical companies for testing their enteric-coated tablets *in vitro* we carried out similar tests in our laboratory.

Figure 3 shows three enteric-coated tablets of ammonium chloride; the three at the right are the original tablet before the test and the three on the left are tablets which had been placed in artificial gastric

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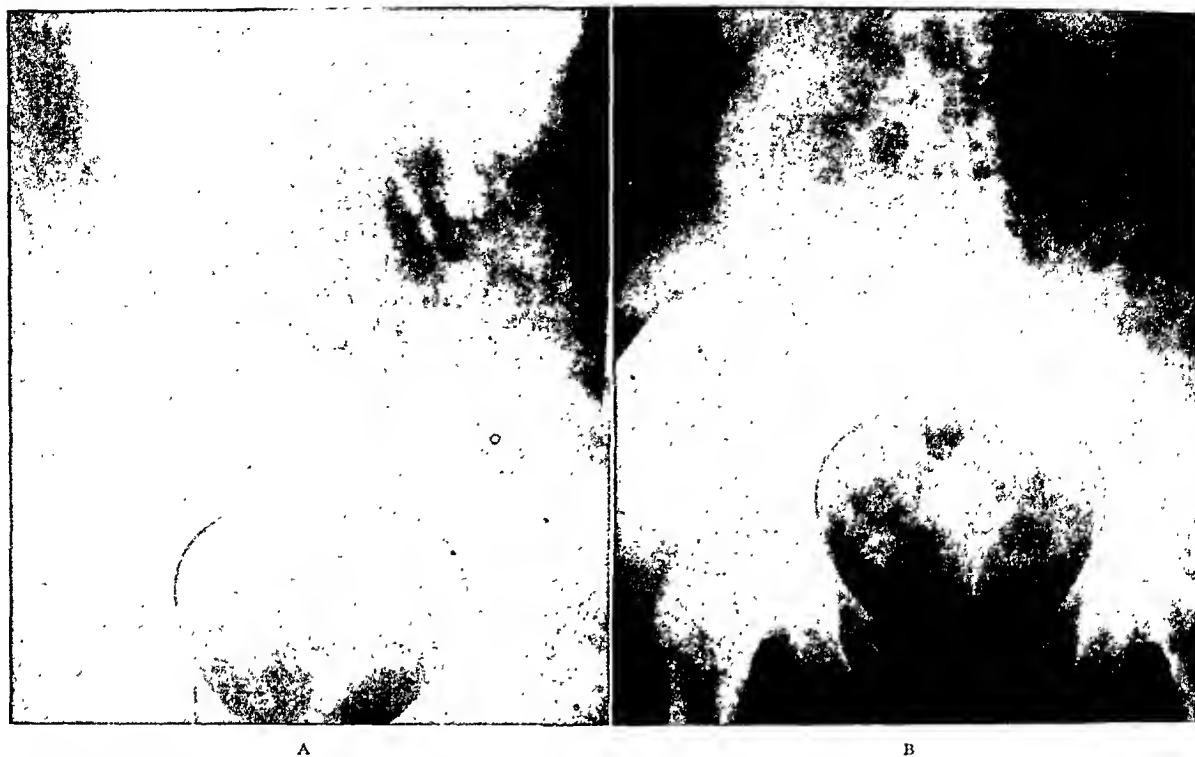


FIG. 2. Roentgenograms of another product. A, immediately after ingestion; B, one hour after ingestion showing complete disintegration.

juice (formula of Toplis) at 38°C. for three hours, and in artificial intestinal juice (formula of Toplis) at 38°C. for four hours. The test showed that during the seven hours in the media the tablets retained 57 per cent of their original weight.

Figure 4 shows the results of our experiment with enteric-coated ammonium chloride tablets put out by another firm. These were placed in artificial gastric juice (formula of Toplis) at 38°C.; at the end of three hours all of the tablets were dissolved and only the coatings were left, despite the firm's claim that their enteric coating protects the drug from action of gastric juice and will break up in the intestines thus preventing gastric irritation.

After this experiment we found that the same thing holds true of enteric-coated digitalis, aminophylline and pancreatin. It was observed clinically that they, too, vary greatly in their disintegrating property, hence making the drug useless if it does not disintegrate at all and thereby depriving the patient of the needed remedy. The inefficacy

of such drugs is only occasionally discovered in general practice.

Many pharmacologists are aware of the fact that the disintegration and the propulsion of enteric-coated tablets depends to a great extent on diet, the rapidity with which the stomach is habitually emptied, the degree of exercise and the degree of gastric acidity as well as upon other individual difference factors. However, the medical practitioner does not bear these facts in mind often enough.

We are particularly interested in calling attention to our experience with enteric-coated tablets for the following reasons: (1) No matter how reputable the pharmaceutical house it behooves the physician to watch carefully for the first forty-eight hours after administration of the drug to ascertain whether or not it has passed through the gastrointestinal tract without disintegrating. This is of particular importance when a drug such as digitalis is administered and when accurate maintenance doses are essential for the patient's well being. (2) There are some preparations on the market which

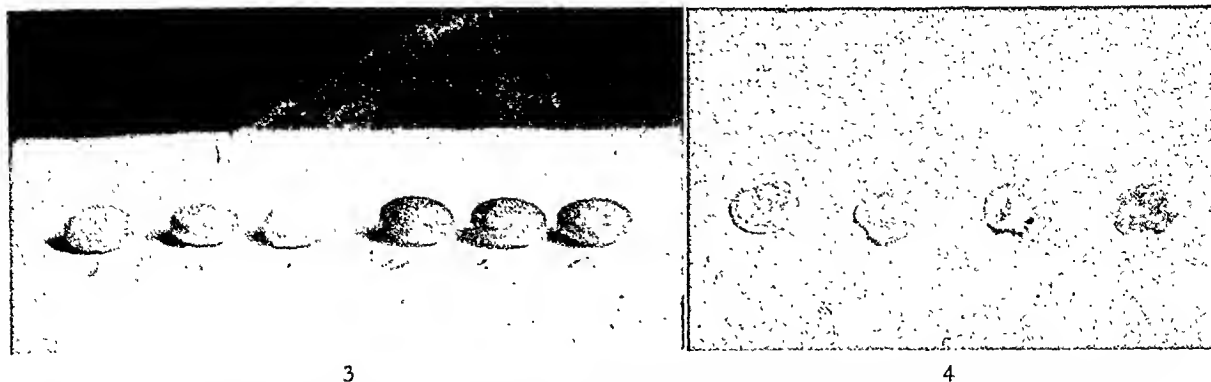


FIG. 3. Enteric-coated tablets of ammonium chloride: right, before *in vitro* test; left, after three hours in artificial gastric juice and four hours in artificial intestinal juice they still retain 57 per cent of their original weight.

FIG. 4. Enteric-coated tablets of ammonium chloride after *in vitro* test. After three hours in artificial gastric juice all tablets were dissolved and only the coatings were left.

in spite of being enteric-coated dissolve in the stomach. If the patient complains of gastric irritation following ingestion of the drug, it may be due to premature disintegration of the drug while still in the stomach. In many of these cases we found that simple vehicles used for the administration of ammonium chloride and other drugs are sometimes tolerated better by patients than when enteric coating is used.

SUMMARY

1. Investigations of enteric-coated drugs have shown that some with coatings which

claim to "protect the tablet from gastric secretions" fail as well to disintegrate in any other part of the gastrointestinal tract.

2. Other preparations disintegrate in the stomach, and in these instances the enteric coating is of no particular value.

3. Clinically, all enteric-coated drugs when administered should be carefully watched for therapeutic effect.

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Status of Antithyroid Substances in Thyroid Disease^{*}

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IN clinical medicine the term "anti-thyroid substance" includes any agent capable of suppressing the formation of thyroid hormone by the thyroid gland. Among such materials are the thyroid hormone itself, iodine, certain thiocyanates, a number of other sulfur-containing compounds, particularly thioureas, thiouracils and sulfonamides and some aminobenzene derivatives devoid of sulfur, particularly *p*-, *m*- and *o*-aminobenzoic acid, *p*-aminophenylacetic acid and *p*-aminoacetanilide. Of these chemicals several are applicable at the bedside for control of conditions due to or associated with an overproduction of thyroid hormone, i.e., to all forms of thyrotoxicosis.

Administration of thyroid hormone to an individual who already has an excess will, it is true, decrease the output of hormone by the thyroid gland of the individual, but it will simultaneously maintain a high level of metabolic activity thus contributing little or nothing to the relief of the thyrotoxic manifestations.

Certain thiocyanates, particularly those of sodium and potassium, have been shown to interfere with the ability of the thyroid to trap iodine and thus with its overall capacity for the formation of iodothyroglobulin.¹⁻³ However, under certain conditions, particularly when the iodine intake is high, this action is uncertain and may be reversed, causing an aggravation of the thyrotoxic state already present. These thiocyanates are, therefore, not applicable to the treatment of patients with thyrotoxicosis.

The exact nature of the beneficial action of iodine in thyrotoxic states is far from clear. That it is capable of relieving, at least temporarily, many of the manifestations of hyperthyroidism in some but not in all patients there is no doubt. It has long been recognized that any agent normally taking part in an enzymic process will, if present in excess, interfere with the reaction. The doses of iodine usually used in the treatment of hyperthyroidism are from 150 to 600 times those normally made available to the thyroid gland. The actual processes through which this suppressive effect is accomplished have not been elucidated but it is clear from the work of Morton, Chai-koff and Rosenfeld⁴ that the administered iodine becomes an active participant in the work of the thyroid cell under such conditions.

Inasmuch as the action of iodine alone is somewhat uncertain, it is now used mainly in an auxiliary or supplemental rôle and will be mentioned further in conjunction with other antithyroid compounds.

The antithyroid substances of most practical importance contain sulfur, held in combination by the radical =N-C-R ,

||
S

in which R is usually —N= but in some instances may be —S— or —O— .⁵ While preparations of the open chain type such as the thioureas are active, closed ring compounds, such as the barbituric acid derivatives and the thiouracils, are much more so.⁶ For instance, propionylthiourea is but one-seventh as active as thiouracil.⁶

^{*} From the New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York, N. Y. Read before the Medical Division of the American Chemical Society at its meeting in Atlantic City, April 17, 1947.

CLINICAL COURSE OF REMISSIONS IN HYPERTHYROIDISM TREATED WITH THIOCARBAMIDE DERIVATIVES

The general pattern of action of all of the sulfur-containing antithyroid drugs thus far used in human beings for the treatment of all forms of thyrotoxicosis is quite similar. However, there are differences in the ease with which control is established, the time required to return the basal metabolism and blood protein-bound iodine to normal and the incidence and severity of toxic manifestations.

Under the influence of adequate doses of any of these compounds one to twelve weeks is the range of time necessary to bring the basal metabolic rate to normal, with an average of from three to five weeks. Subjective improvement usually occurs in from five to seven days. Nervousness is the first symptom to disappear in approximately one-half the patients.

As observed in 298 subjects, of which 193 had Graves' disease and 105 toxic nodular goiter, relief was first noted with the disappearance of one of the following manifestations, mentioned in the order of their frequency: apprehensiveness, insomnia, loss of weight, palpitation, systolic blood pressure above 150 mm. Hg and voracious appetite.

In the course of treatment toxic reactions may appear. These vary in frequency and severity depending upon the particular thiocarbamide derivative used. In the present studies an overall incidence of reactions to thiouracil occurred in approximately 13 per cent of all subjects, and to propylthiouracil in less than 0.5 per cent. Severe reactions necessitating the discontinuance of therapy included agranulocytosis, febrile urticarial reactions and jaundice (?). Complete agranulocytosis has been observed in about 2.5 per cent of all subjects given thiouracil and in none of those to whom propylthiouracil has been administered. Jaundice has been reported but the direct connection between its appearance and the use of a thiourea

derivative has not been conclusively established. All fatalities have been attributed to either agranulocytosis or jaundice. Among the other toxic symptoms which may have called for an adjustment of dosage but not for the cessation of treatment have been headache, nausea, vomiting, swollen salivary and cervical glands, various types of rashes and edema of the ankles.

Following the complete control of the thyrotoxic state with an antithyroid drug, the systemic disturbances which remained in our patients were two-fold in nature: (1) permanent alterations in the thyroid, eye, heart and/or pancreas, directly traceable to the pre-existing thyrotoxicosis and (2) effects upon the thyroid and eye, possibly attributable to the treatment. It is with the second group that we are herein primarily concerned.

A decrease occurred in thirty-nine of 102 patients who initially showed exophthalmos. In three of these an aggravation of the condition has been observed. This has been relieved but not cured in two patients by the simultaneous use of maintenance doses of the antithyroid preparation, small doses of iodine (Lugol's solution, 1 minim daily or every other day) and varying amounts of desiccated thyroid substance (0.25 to 1.5 gr.) daily. In the third patient submaintenance doses of propylthiouracil have been employed and a mild thyrotoxic status allowed with a concomitant recession, but not remission, in the exophthalmic manifestations.

While under treatment with thiouracil,* 130 of 164 patients with initially enlarged glands were observed for variations in size. No actual measurements were attempted, but the impressions of the patient and his family and the independently recorded impressions of at least two observers were made the basis for the collection of the data. A decrease in size occurred toward the end of the first month of treatment in thirty-one

* Generous supplies of thiouracil and propylthiouracil have been made available through the courtesy of Dr. Stanton Hardy, Lederle Laboratories, Pearl River, N. Y.

of 103 patients with a Graves' type of disease, or toxic hyperplasia, and in twelve of sixty-one with a Plummer's syndrome, or toxic adenoma. At approximately three months in the former group and five months in the latter, twenty-four and twenty-one subjects, respectively, showed a definite increase in the size of the gland. No changes were observed in the configuration of the thyroid at any time in 42 of the 130 persons studied. Does the initial decrease in size correspond to the final "emptying out" of stored colloid and the later enlargement to hyperplasia "permitted" by the unopposed action of the thyroid-stimulating hormone of the pituitary?

In eighteen patients with enlarged thyroids, the toxicity of which has been controlled with propylthiouracil, we have concomitantly used a supplement of Lugol's solution, 1 minim daily. In three of these a further enlargement has been observed. This is a lower incidence than was observed in patients under treatment with thiouracil or propylthiouracil in whom iodine supplements were not used. The iodine supplement was begun as soon as the patient's basal metabolic rate was plus 20 per cent or below. It was continued until the thiocarbamide derivative was stopped although more or less arbitrarily the frequency of dose was often decreased to twice weekly for two or three months before it was completely omitted.

The group is too small for statistical analysis. However, there seems to be some justification for raising the question of the possible rôle of iodine as a useful adjunct in our management of hyperthyroidism with thiocarbamide derivatives. Calculated on a weight for weight basis the doses of iodine we have used correspond well to those in the rat which McGinty⁷ has shown prevents the increase in weight produced by thiouracil. However, the amounts of thiouracil used by McGinty estimated on a similar basis were six or seven times those used in the human being. Nevertheless, it seems that his conclusions may hold for the thyrotoxic patient as well as for the normal

rat, namely, that this action of iodine may be due not "to any toxic effect of iodide but to diminished sensitivity of the thyroid cells to thyrotropic stimulation." Astwood's observation⁸ that sudden diminution took place in the size of the thyroid gland when iodine was administered in the course of thiouracil therapy is further confirmation in the human being of an action similar to that seen in the rat. Other observations by the same worker suggest that under some circumstances therapy with iodine and propylthiouracil may be factors in increasing the size of the thyroid.⁹

In preparation for surgery we use still larger doses of iodine, 250 to 375 mg. daily (30 to 45 minims of Lugol's solution), for periods up to three weeks without being able to detect any escape from the effects of the concomitantly employed thiouracil. Contrary to the practice of some of the larger clinics we continue thiouracil until the day before operation. That this does not interfere with the "colloid packing by iodine" is clearly shown in Figure 1, a microscopic section of the operative specimen removed from a man, forty-three years old, suffering from a Graves' type of goiter with a pretreatment basal metabolism of plus 73 and a preoperative value of plus 1. Undoubtedly a thyroid hormone-poor colloid with a high titer of iodine exists here as in the experimental animals subjected to nearly identical treatment with thiouracil and iodine.⁷

"PERMANENT" REMISSIONS FOLLOWING USE OF THIOURACIL AND PROPYLTHIOURACIL

The medical course of forty-three of seventy-one patients seen during the first year that thiouracil was available for our use has been followed to date. Fourteen are still under treatment. In the remaining twenty-nine (67.4 per cent) no drug has been administered for periods of from eighteen to thirty-seven months. It is believed that these can be looked upon as "cures." They are as likely to have recurrences, as other patients who have had

repeated bouts of thyrotoxicosis, whether operated upon or not.

Similar studies have not been completed in relation to treatment with propylthiouracil or for propylthiouracil in conjunction with iodine. However, the impression is gained from a preliminary review of available data that a small dose of iodine (8 mg. or less daily) added to the regimen after the thyrotoxic state is controlled may materially increase the number of permanent remissions.

INFLUENCE OF IODINE UPON THE ACTIVITY OF SULFUR-CONTAINING ANTITHYROID COMPOUNDS

The rôle of iodine in the management of thyrotoxicosis is not clear, nor is its effect upon the goitrogenic activity of sulfur-containing antithyroid compounds fully elucidated. Several points can be made: (1) A diet low in iodine markedly enhances the goitrogenic effect of thiouracil and similar compounds.^{5,7} (2) When potassium iodide is added to the drinking water of thiouracil-treated rats in amounts ranging from 10 to 1,000 mg. per liter, there is slight inhibition of the goitrogenic effect but a rapid marked increase in the water-soluble iodine content of the thyroid gland.^{5,7,10} Indeed, a single intraperitoneal dose of potassium iodide has caused the iodine concentration within the thyroid to return half way to normal within fifteen minutes. The amount of inorganic iodide thus trapped by the thiouracil-treated thyroid is roughly proportionate to the amount of iodine given. This iodine, however, remains in an inorganic form. (3) It is reported that pretreatment of thyrotoxic patients with large doses of iodine for periods varying from several days to several months slightly retarded onset of the inhibiting action of thiourea but increased its ultimate activity some threefold.¹¹⁻¹³ (4) Iodine in moderate dosage used concomitantly with thiouracil or some of its derivatives may decrease the frequency of relapses. (5) Excessive amounts of potassium iodide interfere with the synthesis of diiodo-

tyrosine and thyroxin by the thyroid gland both *in vitro* and *in vivo*.⁴

No hard and fast conclusions can be drawn from these facts but some statements may be thought-provoking: (1) Sulfur-containing antithyroid compounds with the possible exception of the thiocyanates only partially prevent the trapping of iodine by the thyroid gland. (2) Pretreatment with moderately large doses of iodine delays the action of thiouracil and its closely allied goitrogens while small to moderately large doses do not influence an already fully established block to the formation of thyroid hormone. (3) Are the effects of iodine entirely related to its importance as a building material for thyroid hormone? This hardly seems likely in view of its capacity for inhibiting the formation of diiodotyrosine and thyroxin when present in excess. Moreover, doses which in toxic hyperplasia decrease the formation of hormone will, in simple iodine-deficiency goiter, increase the functional activity of the gland even to the point of causing thyrotoxicosis. Rawson et al.¹⁴ and Danowski, Man and Winkler¹² believe the hyperplasia of thyrotoxicosis is reduced by iodine through its ability to inhibit the stimulating action of the thyrotropic hormone of the pituitary (TSH). Astwood¹⁰ believes this action results not in decreased capacity of the pituitary for forming TSH but rather a depression of the action of TSH itself. (4) It seems likely that iodine in small doses should be used routinely in conjunction with thiouracil treatment of hyperthyroidism in an effort to determine an optimal dosage for the favorable influence that the combination has been shown to exert, at least in some cases and under some circumstances.

CHOICE OF ANTITHYROID DRUGS IN HYPERTHYROIDISM

Of more than 300 sulfur-containing compounds studied in animals^{6,15-17} a little less than one-half have shown some detectable activity and twenty-five have proved to be active or more active than thiouracil.¹⁷

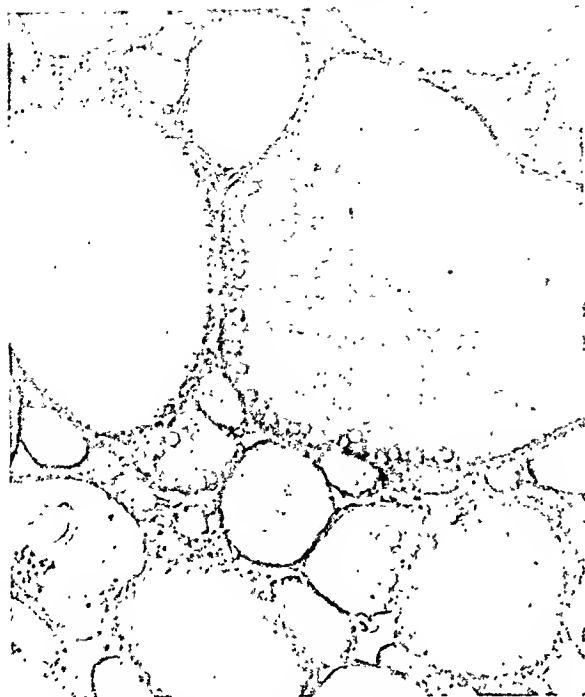


FIG. 1. Microscopic section of specimen obtained at operation (low power). A man, fifty-two years old, who first showed symptoms of Graves' disease without thyroid enlargement three months before he came under treatment. Prior to surgery the patient was treated for approximately eleven months with thiouracil and for seven months with propylthiouracil. The condition was fully controlled. However, the patient continued to have attacks of paroxysmal auricular tachycardia. Fifteen days prior to operation Lugol's solution, 15 minims three times a day, was added to the regimen. Note practically complete involution with large colloid lakes.

Of these twenty-five, five have come to clinical trial in the human being: 2-thiouracil, 6-methyl-2-thiouracil,¹⁸⁻²⁸ 6-ethyl-2-thiouracil,⁵⁻²⁹ 6-*n*-propyl-2-thiouracil³⁰⁻³⁷ and 5, 5-diethyl-2-thiobarbituric acid (thiobarbital).^{5,29,35,38,39} Four compounds, less active in the rat than thiouracil, have also been applied to the management of hyperthyroidism in human beings: thiourea,^{11-13, 20,27,28,40-56} tetramethyl-thiourea,⁵⁷ diethyl-thiourea⁵⁷ and 2-aminothiazole.⁵⁸⁻⁶⁸

The antithyroid activity of the nine substances just mentioned has been compared in rats and human beings. (Table I.) The activity index as determined in rats is that devised by McGinty and Bywater.⁶ The activity in terms of thiouracil in human beings with thyrotoxicosis is derived from the average doses necessary to relieve the

cardinal symptoms and signs of the disease and to normalize the basal metabolic rate and the protein-bound fraction of iodine in the blood. Thus, the activity index as described for human beings is far less accurate than that derived for the rat.

TABLE I
ACTIVITY INDEX OF ANTITHYROID COMPOUNDS

Substance	Activity Index (Thiouracil = 1.0)	
	Rats	Human Beings
Diethyl-thiourea.....	0.40	Too Toxic
Thiourea.....	0.10-0.12	0.3
2-Aminothiazole.....	0.15	1.0
Tetra-methyl-thiourea.....	0.30	1.0
2-Thiouracil.....	1.00	1.0
Thiourea plus iodine.....	1.3
Thiobarbital.....	1.45	2.0
6-Methyl-2-thiouracil.....	1.15	2.0
6- <i>n</i> -Propyl-2-thiouracil.....	11.00	2.0-3.0
6-Ethyl-2-thiouracil.....	8.00	2.0-4.0

However, probably neither represents the total picture of the activity of any given compound for factors concerned with duration of action, dosage level at which activity is most pronounced, toxic manifestations, etc. are either partly or wholly neglected in such evaluation. Despite these shortcomings a fair clinical appraisal of the action of each drug can be reached.

In Figure 1 a comparison is made between the therapeutic effectiveness and the toxicity of the eight thiocarbamide derivatives which have been successfully used in human beings for the control of thyrotoxicosis. The only other drug of this group thus far employed in hyperthyroidism, diethyl thiourea, has been omitted from this illustration because of its toxicity. In each of the four patients upon whom it was tried severe toxic symptoms occurred when 0.6 Gm. were given daily;⁵⁷ however, such a dose was insufficient to relieve the manifestations of the coexisting thyrotoxicosis.⁵⁷

The therapeutic activity of thiouracil has been placed at 1.0 and an attempt made to evaluate the usefulness of other drugs in terms of this arbitrary standard. (Fig. 2.)

In order to evaluate each drug fully some brief reference to the data of individual workers seems necessary.

Thiourea alone has been used in more than 375 patients^{11-13,20,27,28,40-56} in initial daily doses ranging from 1.0 to 3.0 Gm.,

improves materially (Fig. 2) although the period of time necessary for control is somewhat lengthened. These workers observed remissions within from one to twelve weeks, with the majority occurring at about the fifth or sixth week of treatment. In

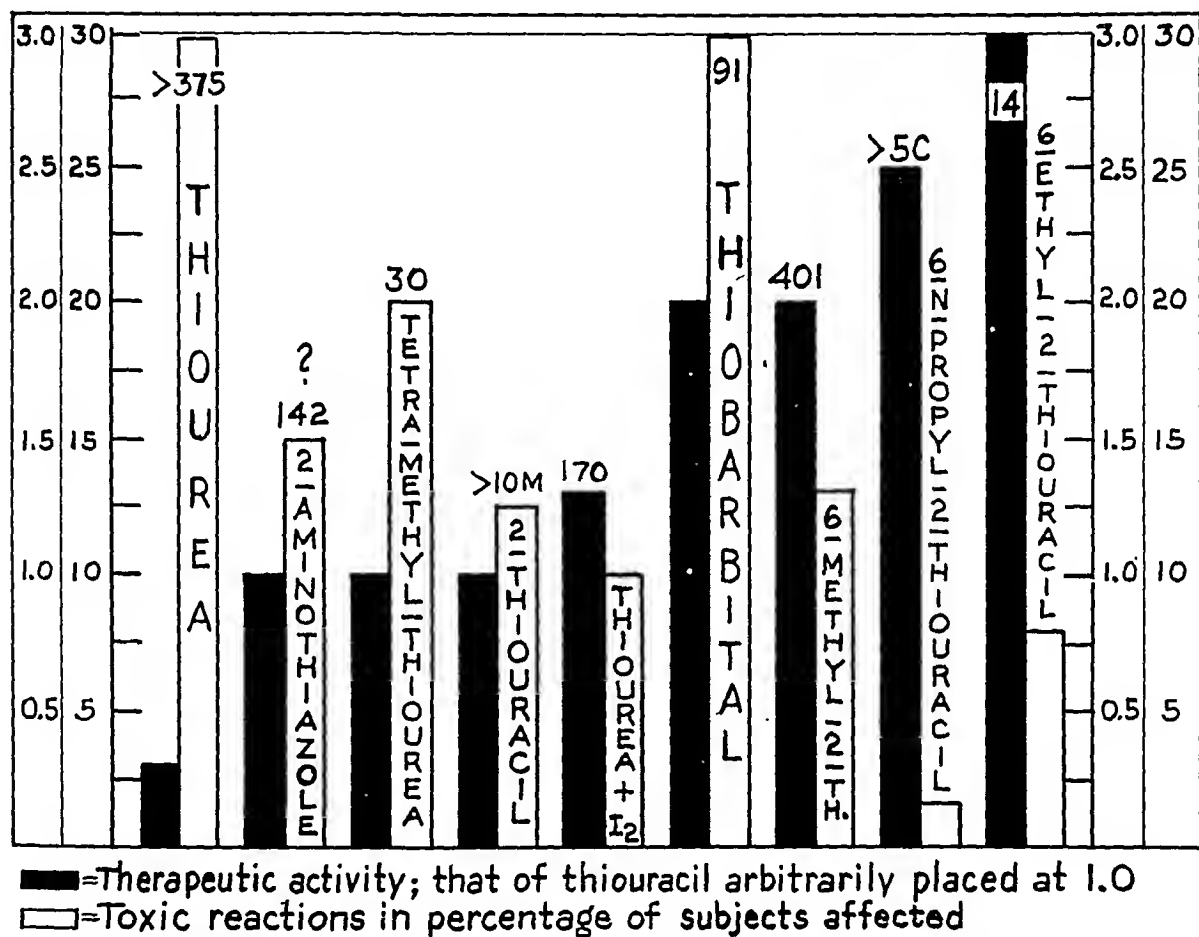


Fig. 2. A comparison of the therapeutic and toxic effects of antithyroid drugs in human beings. Numbers at top of each column represent number of subjects upon which data are based.

and maintenance doses from 0.3 to 1.0 Gm. On the average, it is approximately 0.3 as active as thiouracil. One worker reports "excellent results without toxicity" when from 0.25 to 0.60 Gm. of the drug are administered daily but gives no details of his investigations.²⁷ In the doses commonly employed the high toxicity (30 per cent) scarcely justifies further clinical trial. However, when the patient is pretreated or concomitantly treated with iodine, as has been done by one group of workers,¹¹⁻¹³ they claim that the efficiency of the drug

their hands initial daily doses of thiourea have varied from 0.05 to 0.28 and maintenance doses from 0.025 to 0.08 Gm. In conjunction with this regimen strong tincture of iodine (U.S.P.) was employed in doses of 15 minims three times daily to yield approximately 440 mg. of iodine each twenty-four hours. As a rule, iodine is begun not less than one week prior to the initiation of the therapy with thiourea, and some patients reported by these investigators had received iodine for many months before the thiourea was added. As a result of their

experiences these workers recommend 0.11 Gm. of thiourea daily in divided doses in combination with the aforementioned dose of iodine, the regimen to be followed "indefinitely." They have observed remissions in 95 per cent of their patients but have seen relapses even after two years of treatment. Toxic symptoms due to the drug were uncommon and could usually be avoided by redistribution of the daily dose. While a careful review of the case reports made by them leaves some doubt as to the absence of toxic symptoms at the end of relatively long periods of treatment, the question of the value of combining iodine in some dose with the thioearbamide regimen certainly warrants further consideration and study.

Tetramethylthiourea, despite a therapeutic activity only slightly lower than that of thiouracil, has proven too toxic to justify extensive clinical trial. In the doses first used (0.2 to 0.4 Gm. daily) the same statement holds true for thiobarbital.^{29,39} However, in many instances control with thiobarbital can be attained by the use of 0.1 to 0.2 Gm. daily³⁸ and the drug has been tolerated in patients who developed reactions following use of thiouracil.³⁸ Perhaps more extensive trial is justified at a lower dosage level, particularly in view of its prolonged action and the rather high incidence of sustained remissions.^{5,39}

Among one group of French workers, 2-aminothiazole has appeared to be a highly effective antithyroid compound, indeed approximately as effective, weight for weight, as thiouracil but 50 per cent more toxic.⁵⁹⁻⁶² However, opinion is sharply divided as other workers have discarded the drug as too toxic to justify further clinical trial.⁵⁸

In the Scandinavian countries, and to a lesser extent in Australia, methylthiouracil has become the antithyroid drug most widely, in fact almost exclusively, used in the treatment of hyperthyroidism.^{19-25,28} It is perhaps one of the most readily manufactured of the more highly efficient goitrogenic compounds. Initial doses have ranged

from 0.06 to 0.90 Gm. daily with an approximate average of 0.2 Gm. daily. The necessary daily amount for maintenance of the patient in remission has varied from 0.01 to 0.30 Gm. with an average of 0.1 Gm. Weight for weight, therefore, the drug appears to be about twice as active as thiouracil although 25 per cent more toxic in effective dosages.

Astwood has made the only published study of results with 6-ethyl-2-thiouracil.²⁹ In fourteen patients he found the drug from two to four times as active as thiouracil and about three-fourths as toxic in effective dosage. Further trial seems to be justified.

Because of its low toxicity (approximately 0.5 per cent) and its high therapeutic activity (2.0 to 3.0), propylthiouracil is fast becoming the antithyroid drug of choice in this country. In this connection attention may well be called to the fact that the addition of any alkyl radicle at C₆ strikingly alters the efficiency of thiouracil. A number of the members of the methane series have thus been tried as a result of which it seems that maximum effectiveness appears when an ethyl radicle is used and a minimum toxicity is achieved with the propyl grouping.

Our own experiences with the antithyroid drugs center about thiouracil⁶⁹⁻⁷² and propylthiouracil.³⁰ The initial daily amount of thiouracil employed has varied from 0.6 to 0.8 Gm. with maintenance doses of 0.1 to 0.3 Gm. If 0.8 Gm. is initially used, this amount is decreased within seven days, irrespective of the clinical condition. If 0.6 Gm. is initially used, it is not continued for a longer period than two weeks when a reduction to 0.4 Gm. or less is made depending upon the status of the patient at that time.⁷⁰ With propylthiouracil, the initial dose now recommended lies between 0.20 to 0.25 Gm. daily. This may be continued in either instance until control is effected. Then a maintenance dose is established which in our experience has ranged from 0.025 to 0.150 Gm.³⁰

In more than 200 patients to whom thiouracil has been administered we have failed to control the hyperthyroidism only in

those (eight in number) who have developed either an urticarial-febrile reaction or a complete agranulocytosis. On the other hand, three of one hundred patients have been difficult to maintain in a controlled state with propylthiouracil; further adjustment of dosage may correct this difficulty, but we have the impression that the overall response may not be quite so dramatic as with thiouracil.

SUMMARY AND CONCLUSIONS

1. Eight sulfur-containing antithyroid compounds have been employed successfully for the control of thyrotoxic states of both the Graves' and Plummer's types: thiourea, 2-aminothiazole, tetra-methyl-thiourea, 2-thiouracil, 5, 5-diethyl-2-thiobarbituric acid, 6-methyl-2-thiouracil, thiourea plus iodine, 6-*n*-propyl-2-thiouracil and 6-ethylthiouracil. There is an increasing antithyroid effect in the order mentioned.

2. Thiourea, tetra-methyl-thiourea, thio-barbital, and probably 2-aminothiazole are probably too toxic in effective dosage to justify further clinical trials.

3. 6-*n*-propyl-2-thiouracil and 6-ethylthiouracil appear to be the most promising members of the group thus far employed in human cases of hyperthyroidism.

4. Iodine in certain doses may enhance the degree of response to thiourea despite its retarding effect upon the rapidity of the action of that and all other drugs of this group.

5. Certain phases of antithyroid activity are discussed, particularly in relation to iodine intake.

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Effect of Injury and Disease on Nitrogen Metabolism*

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A NORMAL full grown animal can be made to store excessive amounts of fat and carbohydrate as fat. Presumably it can utilize for the same purpose non-nitrogenous fractions of the amino acids, but it has no similar capacity to store the nitrogenous fractions of these compounds. Under ordinary circumstances the adult animal excretes daily as much nitrogen as it ingests. When the protein of the diet is increased, excretion of nitrogen in the urine for a brief interval falls short of the intake. This slight retention may represent only the amount required to accelerate the metabolism and excretion of nitrogen. Impairment of renal function may also cause temporary retention of nitrogen, not as protein, but as non-protein nitrogen. It has been generally accepted that a sustained positive nitrogen balance is evidence, and the only unequivocal evidence, that an adult animal has been depleted of protein. This is, of course, not true of the growing animal which retains nitrogen for the formation of new tissue. It is reasonable to assume also that hypertrophy of muscles and other organs must be attended by retention of nitrogen for the formation of protein. Recently it has been demonstrated that testosterone may promote economy in the use of protein. Under its influence the adult animal will store limited amounts of protein.¹

When the quantity of protein in the diet is greatly diminished, the amount of nitrogen excreted falls accordingly with only a slight lag for a certain time. A point is ultimately reached, however, when the

excretion falls less rapidly than the intake; the animal goes into negative nitrogen balance. As the reduction of protein is continued this loss of nitrogen increases but the actual quantity of nitrogen excreted diminishes. The catabolism of protein decreases to a minimum when an animal is receiving a diet that contains adequate calories but no protein.²⁻⁵ With such diets the urinary nitrogen excretion of a human adult has been reduced to as little as 0.03 Gm. per Kg. per day, equivalent to 0.2 Gm. of protein.²⁻⁵ Such low figures cannot be attained so long as the subject receives any protein, save possibly under circumstances that will be described later. The amount of protein required, both to maintain nitrogen equilibrium and to attain minimum nitrogen excretion, will depend upon the caloric value of the diets given. Body protein is used most conservatively when there is a generous supply of calories. A certain proportion of this must be supplied as carbohydrate but the major portion may be provided equally well as fat. Muscular activity does not appear to necessitate the expenditure of protein, provided a sufficient excess of carbohydrate and fat is given.^{6,7} The calorogenic effect of thyroid can also be met with carbohydrate and fat.^{3,4,8} The protein which is destroyed in the state of minimum nitrogen metabolism is apparently not spent for the production of energy.

✓ The phenomena that attend deprivation of protein alone differ sharply from those that attend starvation. In the latter condition nitrogen excretion does not diminish to the same degree. At the end of thirty-one

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days Benedict's⁹ fasting man was still excreting 7.2 Gm. of nitrogen, equivalent to 44 Gm. of protein, per day while after twenty-four days on a high calory diet containing less than 1 Gm. of nitrogen daily, Smith⁵ excreted only 2.54 Gm. of N, equivalent to 16 Gm. of protein. This difference can be attributed partly to the lack of carbohydrate in the metabolism mixture of the starving subject. In the first three days after the period of starvation when Benedict's subject took only carbohydrate, the urinary nitrogen fell to 3.8 Gm. daily, a little more than one-half of what it had been during starvation. Presumably the extra protein is used for production of carbohydrate when this is not supplied in the diet. In another respect the nitrogen excretion of the starving subject differs from that of the person who subsists on a protein-free diet. The starving subject loses no nitrogen through the bowel because he does not defecate. Defecation does not cease nor does fecal nitrogen diminish to any great extent when protein is removed from the diet. During the control period, on a diet containing 13 Gm. of nitrogen, Smith excreted 1 Gm. daily in his feces. During the twenty-four days in which his diet contained an average of only 0.65 Gm. of nitrogen the feces contained an average of 0.82 Gm. per day.

When the quantity of protein in the diet is altered, the various nitrogenous components in the urine do not change proportionally. Urea and ammonia, especially the former, are most affected; the other compounds in the urine change very little. In the course of twenty-four days the urea nitrogen in Smith's urine fell from 10.20 to 0.32 Gm. per day, or 97 per cent; ammonia nitrogen from 0.50 to 0.20, or 60 per cent while the remaining nitrogen diminished from 0.151 to 0.112 Gm., only 26 per cent. Urinary urea and ammonia are the most completely oxidized products of protein metabolism. They may be regarded as representative of the protein that has been utilized for the production of energy. Creatinine, uric acid and the other com-

pounds that make up the remainder of urinary nitrogen appear to have more specific and indispensable purposes.

Minimum protein metabolism Folin termed endogenous metabolism, which he conceived as the result of irreducible wear and tear of the proteins of the body. It seemed to be implied in this concept that the streams of endogenous and exogenous protein metabolism were distinct. Except for the small fraction that was used to replace the quantities worn out by the endogenous processes, the exogenous protein was diverted to combustion. From the gross standpoint of overall accounting this concept is unimpeachable; from the standpoint of the individual components of the diet it is altogether untenable. Schoenheimer¹⁰ by means of amino acids tagged with heavy isotopes showed that the products of exogenous protein become inextricably mixed with endogenous compounds. Not only are fragments of amino acids exchanged but proteins appear to pick up amino acids from their environment. The isotopic technic has also greatly advanced knowledge of the specific functions of amino acids. Besides their general function in the formation of various types of proteins, certain fractions of the amino acids are used for formation of nitrogenous compounds that are required for the conduct of special metabolic processes. It has been discovered that certain of the amino acids must be supplied from extraneous sources while others can be synthesized in the body.

Of the amino acids found in the body nine are now recognized as essential, i.e., beyond the synthetic capacity of animals.¹¹ These are: threonine, valine, leucine, isoleucine, lysine, phenylalanine, tryptophane, histidine and methionine. Arginine should probably be added to this group. It is apparently synthesized but not with sufficient facility to meet the requirements.¹¹ These amino acids have been termed essential because they must be supplied preformed in the diet. In a broader sense, however, all amino acids are indispensable, some more directly than others. Cystine

and tyrosine can be synthesized only from the essential amino acids methionine and phenylalanine, respectively. Consequently, if cystine and tyrosine are not provided preformed, sufficient excess of methionine and phenylalanine must be supplied to yield the necessary amounts of cystine and tyrosine. An animal given a diet that contains an adequate amount of protein that is deficient with respect to one or more of the essential amino acids fails to grow, loses weight and ultimately succumbs. It wastes nitrogen throughout this process of deterioration. Such deficiencies may be absolute or relative. If the protein is not altogether devoid of any essential acid, the deficiency may be overcome by administration of large enough quantities of the protein to provide adequate amounts of the amino acid. It is impossible under these circumstances to achieve any economy in the use of protein. Among the features that determine the nutritive efficiency of a protein are the proportions of the various amino acids of which it is composed. The optimum proportions for growth and maintenance have been only roughly ascertained.

It is becoming evident that deficiencies might arise from endogenous as well as dietary causes. Disorders or diseases may interfere with proper utilization of an amino acid for an essential purpose, for example, the formation of cystine from methionine, or may create an unusually large demand for some particular derivative of one of the amino acids, for example, the methyl group of methionine. The existence of such deficiencies, while not conclusively demonstrated, is tacitly implied in the use of cystine and methionine for the treatment of disorders of the liver, nephrosis, etc.

It has been stated that minimum protein metabolism can be attained only if an animal is given large amounts of fat and carbohydrate with no protein. Millard Smith,⁵ after twenty-four days on a diet containing less than 1.0 Gm. of nitrogen daily, had lost 94 Gm. of nitrogen, or 590 Gm. of protein. In spite of this, when he was

given a regular diet at the end of the period, his nitrogen excretion rose from less than 3 Gm. per day to about 8 Gm. In the course of this experiment Smith's protein stores had been only moderately depleted. He could still be regarded as a well nourished individual. When an animal has been reduced to a state of severe malnutrition by deprivation of protein, it can apparently utilize protein with greater efficiency.¹²⁻¹⁴ The growing animal seems to be able to achieve a similar economy.³

Although a sustained positive nitrogen balance is accepted as practical proof of previous protein depletion, failure to establish a positive balance does not exclude antecedent protein depletion. In fact, *per se*, it gives no precise information about the past. It may indicate, as has been previously mentioned, that the subject is receiving too few calories or protein that is deficient in quantity or quality. On the other hand, it may indicate that the subject is suffering from some one of the many disorders that give rise to the condition long known as "toxic destruction of protein." As much as sixty years ago (Shaffer and Coleman)¹ Friedrich Müller showed that patients with typhoid fever lost comparatively large quantities of nitrogen in the urine. The phenomenon was carefully studied by Shaffer and Coleman,¹⁵ Koehler,¹⁶ DuBois and associates¹⁷⁻²⁰ and others. Subsequently, it has been found that similar destruction of protein follows acute hemorrhage,^{21,22} operations and injuries²³⁻²⁶ and a variety of other conditions.

Koehler¹⁶ showed that a normal person subsisting on a diet containing minimal amounts of protein, but high calories, could perform heavy muscular work without any increase of urinary nitrogen, but the nitrogen excretion of patients with febrile diseases could not be reduced to a minimum by similar diets. DuBois and associates¹⁷⁻²⁰ could not prevent losses of nitrogen in such conditions by administration of diets containing adequate amounts of protein and calories far in excess of the needs of the patients. The degree and duration of the de-

struction of protein seem to vary with the severity of the injury or disease^{16-20,26,27} if the term "severity" is loosely defined. The critical features that determine the uneconomical use of protein have not yet been identified. Nitrogen losses can be prevented without difficulty after the repair of inguinal hernias but not after appendectomies. Negative nitrogen balances regularly follow major fractures but nitrogen equilibrium is easily established after osteotomies.^{27,28} Grossman et al.²⁷ found that in meningococcus meningitis and in scarlet fever, treated by sulfonamide drugs, negative nitrogen balances frequently continued despite high protein diets, after the temperature had become normal and symptoms and signs of the disease had been abolished. The losses of nitrogen appeared to be related to the inherent gravity of the disease, not to its clinical manifestations. It is evident from these observations and studies of fractures²⁸ that fever is not responsible for the wastage of protein.

Protein is used in this profligate manner after injury only by previously healthy persons. Moreover, this reaction to injury appears to be self-terminative. After it has continued for a certain length of time the loss of nitrogen gradually diminishes. Ultimately, provided that an adequate diet is given, a positive nitrogen balance can be established, even if the disease or injury continues. Shaffer and Coleman¹⁵ and Coleman and DuBois¹⁷ established positive nitrogen balances during relapses in three of their patients with typhoid fever, although they had been unsuccessful in the earlier stages of the disease. If they can be made to eat, patients with tuberculosis²⁹ and other chronic infections²⁷ will store protein. Browne and associates³⁰ have suggested that the early stage in which protein is wasted should be termed the catabolic phase of injury, the later stage in which protein is stored the anabolic phase. They found that during the anabolic phase renewed injury caused little waste of nitrogen.

Shaffer and Coleman¹⁵ were unable in

most instances to prevent losses of nitrogen during the early stages of typhoid fever. They were, however, able to influence these losses by varying the caloric value of the diets they gave. Nitrogen excretion was distinctly greater when the diets contained less than 2,000 calories than it was when the diets contained 3,500 or more calories. The losses of protein were not inversely proportional to the calories given but when the caloric intakes fell below the daily energy requirements extra protein was expended. The protein-sparing effect of calories has also been demonstrated by Brunschwig et al.²⁴

Whether or not wastage of protein after injury can be mitigated or abolished by dietary measures has been a subject of controversy. Differences of opinion can undoubtedly be attributed partly to failure to recognize the conditioning features which have been previously mentioned. It is obvious that in the analysis of data both the severity and duration of the injury must be considered. In the studies of typhoid fever by Shaffer and Coleman,¹⁵ for example, it is impossible in most instances to decide whether a change of nitrogen metabolism is referable to dietary regulation or to the course of the disease. In none of the earlier experiments by Coleman, DuBois, etc.^{1,3-5} were positive nitrogen balances established in the most acute stages of the diseases studied. The quantities of protein employed by these investigators, however, were not large according to present standards although they were deemed extremely generous in an era in which protein in disease had a noxious reputation. Attempts to give these quantities were often thwarted by anorexia and digestive disturbances. The effect of feeding large quantities of protein was not, therefore, subjected to rigorous examination. With a more tolerant attitude toward protein and with concentrated preparations of easily assimilable and highly nutritious proteins, it became possible to reopen the investigation in a less restricted manner. The obstacle of anorexia was removed by the development

of hydrolysates of protein suitable for intravenous administration.

With these aids, Grossman et al.²⁷ were quite unable to establish nitrogen equilibrium even with large amounts of protein and high calories in patients with severe acute infections or after serious injuries or operations. Howard,^{26,28} Browne³⁰ and their associates were equally unsuccessful. By giving large quantities of mixtures of amino acids or hydrolysates of protein Madden and Clay³¹ produced positive nitrogen balances in a certain proportion of dogs with sterile abscesses induced by injections of turpentine. Such lesions are, however, relatively trivial and of short duration. Hirschfeld and his associates,³² by giving 150 or more Gm. of protein and over 4,000 calories per day, succeeded in establishing positive nitrogen balances almost from the beginning of treatment in some burned patients, but they failed in others. The same inconsistency is evident in the series of cases presented by Elman³³ and by Brunschwig et al.²⁴ In Elman's series some of the patients were obviously chronically ill and wasted. In all cases an interval of four to six days elapsed between the injury and administration of protein hydrolysates. This is the period in which the greatest losses of nitrogen have been observed.^{24,27} The success of Mulholland, Co Tui et al.²⁵ in conserving protein after gastrectomy by means of protein hydrolysates may have been referable to the fact that these operations were performed chiefly on chronically wasted patients. For similar reasons many other reports must be discounted. Studies of persons with large exudative lesions must also be rejected unless the quantities of nitrogen lost in the exudates are measured. This criticism applies to the positive balances reported by Cope and associates³³ in burned persons.

Cuthbertson²³ found that nitrogen excretion immediately after operation was not great but became considerable after three or four days. This was confirmed by Grossman,²⁷ Peters and associates³⁴ and by Howard²⁶ after fractures. This increase may

be apparent rather than real; it may be related only to the protein intake which is minimal immediately after an operation or severe injury. When Grossman et al.²⁷ gave protein hydrolysates equivalent to 75 Gm. of protein intravenously on the first two postoperative days, the negative nitrogen balances did not differ appreciably from those of patients who received no protein. The extra nitrogen from the hydrolysates was apparently wasted in the urine. In Shaffer and Coleman's¹⁵ cases of typhoid, negative nitrogen balances seldom exceeded 12 Gm. daily at the height of fever. In only one case, in which attempts at feeding were ineffectual, was the negative balance extremely large. In this instance the excessive waste of protein may be attributed to deficient calories. Injury appears to provoke no malicious destruction of protein but to compel the expenditure of a certain amount of tissue protein. Insufficient calories will increase these losses but administration of extra protein does not seem to diminish them. Whether by administration of extremely large quantities of protein and calories the native protein can be spared is still a debatable question.

If this disorder is an inevitable reaction to injury, it may be of no advantage to try to correct it, at least immediately after operation. Hirschfeld, Abbott et al.³² did, in fact, find that early administration of large amounts of protein to burned patients provoked nausea, vomiting, diarrhea and other untoward symptoms. After the first few days, however, patients were able to take large quantities of protein without deleterious effects. Since the reaction to injury is self-terminative and its duration unpredictable, generous amounts of protein should be given early enough to anticipate the anabolic phase; generous calories should be provided as early as possible to minimize the losses of body protein. The impression has been voiced that high protein diets improve the sense of well being and hasten the appearance of the anabolic phase. Such impressions are hard to evaluate. There can be no doubt that high protein

diets accelerate the restoration of body protein once the anabolic phase has begun. The patient who is suffering from chronic diseases or incurs an acute injury while in a state of debilitation deserves high protein and calories from the start because he can use protein efficiently.

It has been suggested that acute injury or disease creates a specific need for extra amounts of some particular amino acid. Croft and Peters³⁵ by administering methionine to rats diminished the nitrogen losses after thermal burns. This reaction cannot be related directly to the injury since methionine has been shown to promote economy of protein in normal animals.³⁶ If the wastage of nitrogen after injury were an expression of the need for extra amounts of some particular amino acid, it should respond more readily to administration of large quantities of protein containing this acid. The partition of nitrogen in the urine does not suggest that protein metabolism is being diverted into abnormal channels. After injury the usual proportion of urinary nitrogen is excreted as urea plus ammonia. Additional dietary nitrogen appears entirely in these forms.^{1,2,14,34} The non-urea nitrogen of the urine does not vary with the nitrogen in the diet. The excretions of creatinine^{1,2,34} and of uric acid^{1,2} are also not consistently affected.

The reaction to injury manifests itself in certain other disturbances that have been less generally recognized. Cuthbertson and Tompsett³⁷ reported that immediately after operations the concentration of protein in the serum fell rapidly. This observation was verified by Peters³⁴ who found that only the albumin fraction of the proteins suffered. This drop, Man³⁴ showed, was accompanied by a similar reduction of serum lipids in which all fractions of the lipids participated. Hypo-albuminemia and hypolipemia in disease have been generally attributed to malnutrition. Although it appears to be well established that serum albumin does fall when an animal is deprived of protein, it is quite clear that current opinions about the general clinical signifi-

cance of hypo-albuminemia must be revised. The precipitate fall of serum albumin after operation cannot be attributed to general depletion of protein. If it were due to malnutrition, it should decline throughout the catabolic phase as nitrogen wastage progresses, but it may even rise appreciably in the face of large negative nitrogen balances.³⁴

Man³⁸ found that during the catabolic phase of the injury reaction the concentration of α -amino acids in the serum was usually low, even if the subjects were receiving high protein diets and had large negative nitrogen balances. This was contrary to expectation. It had been anticipated that the amino acids of the serum would reflect the rate of turnover of protein. It was further discovered that, like serum albumin and lipids, amino acid nitrogen fell sharply after operations. It had already been found that it was low in certain infectious diseases³⁹ and in the abdominal crises of the nephrotic syndrome.⁴⁰

These phenomena appear to be an integral part of the reaction to injury. Like the wastage of body protein the reductions of serum albumin, lipids and amino acids appear only in patients who were previously in a healthy condition. In patients debilitated by chronic disease these components of the serum, usually already low, do not fall further or fall only slightly after an operation. In healthy persons the extent of their decline varies with the gravity of the operative procedure. The explanation and significance of these phenomena has not been elucidated. What useful purpose they may possibly serve is not apparent. Injury seems to dislocate the metabolic processes profoundly. The disturbance is characterized by impairment of the synthesis of protein, including serum albumin and a tendency to route products of protein metabolism preferentially to urea and ammonia.

Since protein is an essential constituent of tissues that cannot be replaced by other foodstuffs, its loss is presumably disadvantageous and should be prevented. Until, however, the nature of the disorder has been

discovered a certain amount of wasting with attendant delay of convalescence and rehabilitation may have to be accepted as an inevitable consequence of severe injuries. Every effort should be made to minimize the losses of protein. In chronic debilitating conditions since the synthetic powers of the body appear to be intact, administration of generous quantities of protein with adequate calories should be a major therapeutic objective. This is equally true in acute pathologic states after the catabolic phase has ended. Since this phase is self-terminative and of variable duration, administration of generous diets should not be delayed until its termination. The anabolic phase should be anticipated. There is no evidence that administration of large amounts of protein during the catabolic phase is injurious. An exception may have to be made of the two or three days immediately following operation. Even if patients cannot be prevented from losing protein during the catabolic phase, the extent of these losses can be reduced to a minimum by administration of large quantities of carbohydrate and fat.

The development of protein hydrolysates suitable for intravenous injection has been a great achievement. With the aid of such preparations, it has at last become possible to administer protein to patients who are unable to eat. It appears to have been established beyond reasonable doubt that nitrogen equilibrium can be maintained and that the protein requirements of normal animals and men can be satisfied by means of properly prepared hydrolysates of efficient proteins. There is, however, no evidence that intravenous injection of such preparations is superior from a nutritive standpoint to the normal method of eating. In fact, all evidence favors the ingestion of whole protein. If hydrolysates are not injected at an extremely slow rate, they provoke nausea and vomiting. In this respect mixtures of pure amino acids might have distinct advantages because, according to Madden and associates,⁴¹ they can be injected in high concentration with great rapidity

without provoking untoward reactions. It would also be possible to vary such mixtures to meet special nutritive requirements. No preparations of pure amino acids suitable for such purposes are, however, commercially available. The slow rate of injection required for hydrolysates limits the amount of protein that can be provided in this form. It also necessitates administration of undesirably large quantities of fluid. In order to administer the equivalent of 75 Gm. of protein with the usual commercial hydrolysates it is necessary to inject 2,000 cc. of fluid over a period of at least four hours. In addition to the protein hydrolysate this fluid usually contains 100 Gm. of glucose, a quantity incapable of supplying the calories required for the day. The total value of such a mixture is only 700 calories. This may be raised to 1,100 calories by using a 10 per cent instead of a 5 per cent glucose solution as diluent; it may be supplemented by additional injections of 10 per cent glucose. Seldom, however, is it possible by these methods to give more than 75 Gm. of protein and 300 to 400 Gm. of glucose, a total of 1,500 to 1,900 calories per day. In order to achieve this the patient must be subjected to a tedious and distressing procedure.

It has been proposed that parenteral hydrolysates be given as supplements to the diets of patients who are able to eat but cannot or will not take enough for their needs. For this purpose such injections are peculiarly unsuitable. The nauseating effects of hydrolysates when given too rapidly have already been mentioned. Even if they are given slowly enough to avoid nausea, patients cannot be induced to eat while they are being injected. Since the injections take so long, they cannot be given during the day without interfering with meals. They must, therefore, be delayed until the evening, thereby interfering with much needed rest.

On the whole, if a patient has no disorder of the gastrointestinal tract that prevents ingestion and utilization of food, it is usually possible to administer more protein and calories by mouth than can be given solely

by parenteral means or with the aid of parenteral supplements. This requires, however, resourcefulness and attention to detail that are seldom given to the subject. This is one of the chief reasons for the excessive use of parenteral feeding; once the needle is inserted the day's ration runs in without much attention. Moreover, the ration comes prepared and packaged so no thought is given to its composition. Diets must be selected with consideration of their nutritive value and the tastes and strength of the patient. It is not uncommon to see a patient staring at a tray, not because he lacks appetite but because he lacks strength and energy to wrestle with the food. Frequently when the tray is taken away, it contains only those foods that demanded effort on his part. Some will eat only if they are fed, others only if the diet is so prepared that it requires no implements other than the hands and a spoon. Unhappily there is a tradition that diets of this kind must be bland, a euphemism for insipid. Lack of physical strength does not necessarily connote disability of the digestive functions. Furthermore, the physical taste and appearance of food are no criteria of their actions in the gastrointestinal tract. Patients who are refused any highly tasty food are frequently given without thought vile tasting or aromatic medications.

In a certain proportion of subjects it is necessary to resort to fluid feedings chiefly or entirely. With the aid of prepared foods, and especially powdered milk, it is possible to make fluid diets highly nutritious and especially rich in protein. When fluid diets are prescribed, advantage should be taken of the sense of thirst as well as the need for nutrition. A full water pitcher need not always be at the bedside. Something more nutritious may be used to allay the desire for fluid. Thirst can even be stimulated by the judicious use of salty fluids if there is no contraindication to the use of salt.

No justification can be found for oral administration of protein hydrolysates, whether it be by ordinary processes of

ingestion or by tube. Co Tui⁴² contends that such preparations are more easily utilized than undigested proteins but this claim is not supported by physiologic observations. Most hydrolysates are so distasteful that oral administration is impracticable. If it were possible to devise less unpleasant preparations, they would still be undesirable. Despite Co Tui's claims, investigations have disclosed that excretion of nitrogen in the feces is greater when hydrolysates are given than when whole proteins are given.⁴³ In fact, some hydrolysates, if given in anything approaching adequate proportions, provoke diarrhea. The reasons for this have not been thoroughly investigated and are not germane to this discussion. It is a general rule that processes of secretion and absorption in the gut are not separable.

One useful application of intravenous hydrolysates is worth mentioning. It is well established that complete starvation inhibits the activities of the gastrointestinal tract and the digestive secretory glands. The starving man has no bowel movements.^{9,44} So long, at least, as there is no obstruction of the alimentary canal, gastrointestinal activity can be abolished by starvation even in the face of severe irritative or inflammatory processes. Under these conditions, however, neither food nor fluids must be introduced into the stomach or gut whereas the normal starving man can apparently take water without inducing bowel movements. In acute mercury poisoning, vomiting and diarrhea cease after a brief interval if the patient is permitted to take nothing by mouth.⁴⁵ If vomiting and diarrhea do not cease upon withdrawal of food and fluids, a local or generalized peritonitis should be suspected (unpublished). Apparently parenteral administration of fluids, including protein hydrolysates, does not provoke gastrointestinal activity. It provides a means, therefore, of preventing or mitigating wasting while starvation and deprivation of fluids are employed to abolish activity of the alimentary tract,

either in preparation for operation or as a means of checking diarrhea.

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Conference on Therapy

Management of Disorders of Cardiac Rhythm

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. J. JAMES SMITH: The internist and the cardiologist spend a good deal of time on the subject which is to be discussed in this conference, namely, the management of disorders of cardiac rhythm. The opening remarks will be made by Dr. Gold.

DR. HARRY GOLD: I should like to suggest that we consider the treatment of disorders of cardiac rhythm under three separate headings: First, there is the treatment of the patient with a chronic or persistent disorder of rhythm, for example, the case of persistent auricular fibrillation or flutter or heart block. Second, there is the problem of the acute attack of disordered rhythm such as the paroxysm of auricular fibrillation, auricular flutter, auricular tachycardia, ventricular tachycardia or heart block. The third problem is the prevention of recurrences of attacks in patients with paroxysmal disorders of rhythm.

The problems of therapy are quite different in these three categories. For example, in the patient with chronic auricular fibrillation one rarely aims at abolishing the abnormal rhythm. One usually tries merely to slow the ventricular rate to normal levels and to allow the patient to carry on with the auricles in fibrillation. In the second category the patients present themselves in the midst of an attack of disordered rhythm, an attack of auricular fibrillation. They may give a history of having had previous attacks but, whether they do or not, the problem before you at the time is that of abolishing fibrillation of the auricles and restoring a normal rhythm. In the third category the patients present themselves with a normal rhythm but are seeking

advice because of repeated attacks of disordered rhythm of one kind or another. The immediate therapeutic problem in these situations is not that of abolishing an attack but of devising a system which will prevent recurrences of whatever kind of attacks the patient is suffering. Obviously these three categories of the problem are not mutually exclusive and in many instances one may be confronted with the matter of not only abolishing the attack that is present at the time but of preventing recurrences in the same person.

I am sure that you are all familiar with the common disorders of rhythm but I list them here to make it easier to discuss them: (1) premature contractions; (2) auricular paroxysmal tachycardia; (3) auricular flutter; (4) auricular fibrillation; (5) ventricular tachycardia; (6) heart block.

It is a matter of the greatest importance to establish the precise diagnosis and to recognize which one of these disorders of rhythm is the presenting problem. When the differential diagnosis is made, it is the unusual case in which one will fail to bring the abnormal rhythm under control by appropriate application of one or another specific drug. In most cases it is fairly easy to establish the precise abnormal mechanism, but there are patients in whom the differential diagnosis is a matter of the greatest difficulty and defies solution even in the hands of the most expert and with the aid of all the special diagnostic devices.

We shall not have the time here to go into the details of differential diagnosis. If we try that, we shall certainly have no time left for a discussion of treatment. What I

should like to do in the two minutes that remain for my introductory remarks is to point out what I believe to be the best procedure in the case of a patient presenting a paroxysm of rapid heart action, whether it be regular or irregular, and in which we do not have the means for establishing the precise abnormal mechanism at work. Specifically, assume that a patient presents himself to you with an attack of rapid heart action, regular or irregular, and suppose that with the methods available at the time, you cannot determine whether the problem is one of frequent premature contractions, auricular tachycardia, auricular flutter, auricular fibrillation or ventricular tachycardia. This is a situation in which the general practitioner finds himself not infrequently. Now assume that you wish to terminate the abnormal rhythm. What should you do? What treatment would provide the best chance of bringing the abnormal rhythm under control without appreciable risk? My suggestion is the use of quinidine. Give the patient 0.6 Gm. (10 gr.) of quinidine sulfate every two hours and examine the heart before each dose. Continue the medication until the attack comes to an end or until the patient develops symptoms of intolerance such as those of cinchonism (blurred vision, tinnitus and impaired hearing) or gastrointestinal symptoms (nausea, vomiting and diarrhea). These minor toxic effects preclude further use of the drug. The two-hour interval is chosen because the maximum effect of any one dose usually develops in this period of time. If the first dose has caused no minor toxic effects, the next dose of 10 gr. is not likely to produce any serious effects. The object is to build the effects of one dose on the effects of the previous one until a level is reached in the body sufficient to terminate the abnormal rhythm. Here is one drug which provides a good chance of bringing under control a fairly large proportion of the patients with any one of five different disorders of cardiac rhythm.

Of course, we are much better off if we are in a position to establish the exact

nature of the abnormal rhythm before treatment is started. That is so because quinidine is not the best choice for all of these five disorders. For example, an intravenous injection of 3 U.S.P. units of an appropriate digitalis preparation, such as ouabain, cedilanid or digoxin, repeated in fifteen to thirty minutes if necessary, may terminate a paroxysm of auricular tachycardia within a few minutes and it may do so with complete safety, whereas oral doses of quinidine may take hours to achieve the same result and the intravenous injection of quinidine is risky except in the hands of those who have had a good deal of experience with its use in that way. I will ask you to bear in mind that the suggestion which I have made concerning the use of quinidine applies only in those circumstances in which the patient has developed an ectopic rhythm and in which for one reason or another the precise nature of the ectopic rhythm is not determined. I hope that the discussion will make clear the best measures for patients in whom the contrary is true, namely, in those instances in which the precise nature of the disordered rhythm is established.

DR. SMITH: Dr. Stewart, would you care to take up the discussion at this time?

DR. HAROLD J. STEWART: Those of us who see a large number of patients with paroxysmal disorders of rhythm find that nodal tachycardia is the most common disorder. This and auricular paroxysmal tachycardia are grouped under the term supraventricular tachycardia. The two are treated similarly.

I was amazed to hear that a paroxysm of auricular fibrillation would need to be treated without a clinical diagnosis. Most of these patients have such a rapid ventricular rate that a large pulse deficit results and the physician should be able to make a correct diagnosis. In auricular flutter one often sees the flutter waves in the neck veins when the patient lies flat and the veins fill up. The examiner is often able to estimate the ratio of the number of flutter waves to the number of ventricular

beats. In paroxysmal auricular tachycardia the rhythm is regular and the rate is constant while in ventricular tachycardia one can hear a little whirr which indicates a slight irregularity, and every now and then a large wave is seen in the jugular vein in the neck when the auricles and ventricles contract simultaneously. In short the physician ought to be able to arrive at a diagnosis in many cases of paroxysmal disorders of rhythm without electrocardiographic aid before treatment is started. Good medical practice requires under most circumstances that one should know what the condition is before one treats it. Many physicians have portable electrocardiographic machines and carry them along when they see a patient in whom there is the emergency of an abnormal rhythm.

I agree that if one does not know the nature of the paroxysm, quinidine may be used with the greatest safety. It is not likely to do any harm in several of the disorders of rhythm whereas digitalis could do harm if the rhythm proved to be ventricular tachycardia.

When the precise nature of the abnormal rhythm is known, the measures which may be used are fairly specific. For a paroxysm of auricular or nodal tachycardia digitalis is, in our experience, more effective than quinidine. First, it is well to try simple measures, such as having the patient take a deep breath and hold it, the Valsalva experiment or have the patient gag himself; if the patient is not too ill, nausea may be induced; these measures will frequently terminate an attack. If these are not effective, carotid sinus pressure may be applied; but in this case atropine ought to be at hand in case the carotid pressure causes prolonged cardiac asystole. The carotid pressure is applied first on one side, then on the other and finally on both sides simultaneously if necessary. We have seen attacks terminated by the additive effect of carotid sinus pressure while the patient is taking a deep breath. Occasionally we use mecholyl subcutaneously in doses of 20 to 30 mg. in young individuals and 30 to 50

mg. in older individuals. Here also, atropine ought to be at hand before mecholyl is given, and it should be injected at once if the patient shows any idiosyncrasy to the mecholyl. Mecholyl is a dangerous drug. It causes many side effects and we do not use it very often. Occasionally we use apomorphine or ipecac to induce vomiting. Finally, if these measures have not proved effective, the patient is digitalized. This usually terminates the paroxysm promptly. One drug should not be used in paroxysmal auricular tachycardia is morphine; if the patient has recurrent attacks, morphine addiction may result.

In auricular flutter we have also found digitalis most effective. It is our practice to digitalize the patient, and it is our experience that it may take more than the usual therapeutic dose of this drug to restore the normal rhythm. If digitalis proves ineffectual after a suitable trial, quinidine may be tried and in a few instances this will restore the normal rhythm.

It is our experience that in many cases of paroxysmal auricular fibrillation with rapid ventricular rate the abnormal rhythm ceases spontaneously when the patient is put at rest and kept quiet. If, however, the abnormal rhythm persists and its prompt termination is indicated, we usually give digitalis to slow the ventricular rate. The normal rhythm might then return, but in the event that the auricular fibrillation still continues, quinidine may be used to terminate it.

The students should be reminded that complete heart block and bundle branch block are contraindications to the use of quinidine.

DR. SMITH: For several days I have been trying to find someone who has had some experience with intravenous procaine in disorders of cardiac rhythm. It has been like trying to find a man who has voted in a Gallup poll. It seems as though the anesthesiologists are one jump ahead of us in this matter. I hope we may have some discussion on that subject.

Dr. Pardee, would you care to make some remarks?

DR. HAROLD E. B. PARDEE: I agree with Dr. Stewart in the matter of diagnosis. I should dislike to think of a situation in which one could not make the differential diagnosis between auricular fibrillation and a paroxysm of auricular tachycardia. All one has to do is to listen to the beat of the heart; one beat is totally irregular and the other is perfectly regular. The rate in a paroxysm of auricular fibrillation may be rapid, perhaps 180 per minute, but as one listens carefully one perceives phases in which the rhythm falters. That does not occur in a paroxysm of auricular tachycardia.

Dr. Stewart referred to variations in the rhythm of patients with ventricular tachycardia. In my experience this irregularity seems to be much talked about but rarely seen in the records. Slight irregularity is occasionally seen in the rhythm of ventricular tachycardia but it is certainly not a characteristic of this disorder.

I want to say a word about carotid pressure, not as a method for treatment but as a method for diagnosis. Carotid pressure is very useful in diagnosis. In auricular flutter, carotid pressure will usually slow the heart, especially if the patient has not had quinidine in amounts sufficient to block the vagal mechanism.

The technic of carotid pressure should be carefully performed. It is not enough to press on the carotid artery. Unless it is properly done, the carotid sheath is merely pushed behind the larynx and the pressure is not effective. If one uses the thumb and presses the artery back against the muscle mass of the vertebral column, one is more likely to secure an effective stimulus. This should be done first on one side and then on the other. Sometimes the pressure on one side, sometimes on the other will terminate a paroxysm of auricular tachycardia. In the case of auricular flutter, carotid pressure does not result in cessation of the flutter but in a marked slowing of the rhythm for a few beats.

Something should be said about the

advisability of giving quinidine to patients in whom an attack of auricular fibrillation has persisted for some days. As Dr. Gold has suggested, one should hesitate to use quinidine in auricular fibrillation of long duration. After a certain time, particularly if heart failure has developed, thrombi appear in the auricles and these may become emboli when the auricles begin to contract with restoration of normal rhythm. It is, of course, true that the same occurs in patients who spontaneously return to normal rhythm but then one cannot help that. In a patient in whom an attack of auricular fibrillation has lasted for forty-eight hours it is inadvisable to use quinidine. In such a case it is best to use digitalis first in sufficient amounts to slow the ventricular rate to the normal range, allowing fibrillation of the auricles to continue.

A word about the paroxysm of ventricular tachycardia. This is the most difficult paroxysm to terminate. It often resists the various measures to which other tachycardias respond. Quinidine in adequate doses should be the first choice. Magnesium sulfate is sometimes useful in ventricular tachycardia. An intravenous dose of 20 cc. of a 10 or 20 per cent solution of magnesium sulfate will sometimes terminate an attack of ventricular tachycardia when other measures have failed.

DR. CARY EGGLESTON: Virtually all the effective and useful measures for controlling the paroxysmal disorders of rhythm have already been mentioned. In the light of Dr. Gold's opening remarks I may draw attention to the fact that in the majority of cases the situation is not one of grave urgency. Of course, it is our desire always to give the patient relief as promptly as possible but, within the range of my experience, there is time in most instances to analyze the patient's condition fairly thoroughly and to determine the precise nature of the mechanism involved.

I think the greatest problem is presented by those patients who come to the doctor with a history of recurrent attacks of severe palpitation. By questioning these patients

one will sometimes unearth a history that permits one to hazard a diagnosis as to the probable mechanism with reasonable accuracy. Statistics are helpful in this regard. We know that the auricular form is far more common than any other form of paroxysmal tachycardia. It gives rise to a regular rhythm. The patient is usually able to sense the difference between regular and irregular rhythm. Our major problem lies in the group in which the patients seek relief from possible future attacks and in which we lack adequate information for a precise diagnosis. As Dr. Stewart has mentioned, I also think that digitalis is very effective in the control of auricular paroxysmal tachycardia; it is less effective in the nodal form. However, I agree with Dr. Gold's opening remarks that in a case in which the diagnosis cannot be made with certainty we should probably resort to quinidine.

I mentioned the fact that in the majority of cases the paroxysms of abnormal rhythms do not present urgent problems, but there are times when the situation is one of immediate urgency. For example, the patient may black out, as he calls it, in these attacks. In my experience I find that this reaction is more likely to occur at the onset or possibly at the termination of an attack than at any other time. In many cases we just have to take our chances and try quinidine. We inform the patient that it is imperative to have an electrocardiogram made at the time of the next attack, no matter what the circumstances, whether it be during the day or night, whether the patient be near or far from the office. The patient should be urged to get to the office, a hospital or a laboratory and have an electrocardiogram taken at once. I might add that one cannot always be certain of the diagnosis even with an electrocardiogram although it is usually most helpful. Once the diagnosis is established one can select rational therapy.

I would like to add to the remarks made on carotid sinus pressure. It is wise to have the patient lying down during carotid sinus pressure because every once in awhile this

procedure will cause syncope. I agree with Dr. Pardee's comments on the technic. I have seen a good many patients in whom the so-called carotid sinus pressure was tried without avail because it was so imperfectly carried out.

Use of digitalis to terminate an attack of auricular tachycardia has already been mentioned. This drug is also useful in preventing recurrences. We can very often carry the patient along satisfactorily for protracted periods of time by the use of fairly large doses of digitalis. We have one patient attending our clinic here who used to be incapacitated by these attacks and now comes in merely for a routine check, with the statement that the paroxysms of auricular tachycardia are only occasional, very brief and not particularly troublesome.

The danger of emboli resulting from the termination of paroxysms of auricular fibrillation has been mentioned. I have not seen any serious embolic phenomena under these conditions. This merely may be a difference of experience in the case of two men. I highly respect Dr. Pardee's opinion in this matter. It has been frequently emphasized that it is inadvisable to terminate a paroxysm of auricular fibrillation by means of quinidine if it has endured for any considerable length of time. Perhaps it is merely good fortune on my part but I have never seen a disaster from bringing such an attack to an end.

DR. SMITH: It might be pointed out that carotid sinus pressure produces its effect as the result of a reflex stimulation of the motor vagal fibers to the heart. The same result, namely, a stimulus passing down the motor fibers of the vagus to the heart, may be obtained in many other ways, such as deep inspiration, straining, pressure on the eyeballs, pulling out of the tongue or more noxious forms of stimulation. Some of these may be more successful than pressure on the carotid sinus.

Dr. Deitrick, when Dr. Gold mentioned the administration of 0.6 Gm. of quinidine every two hours, I saw a cloud cross your face. I think you were concerned with the

question as to what Dr. Gold would do when he encountered a case in which the quinidine caused cardiac standstill. Would you care to join the discussion at this point?

DR. JOHN B. DEITRICK: It is perhaps unfortunate, although in a conference like this it is unavoidable, that discussion of the treatment of disorders of rhythm is divorced from a consideration of the underlying disease processes which bring them about. I am sure you all will agree that the management of these patients is not merely a problem of juggling a few drugs.

Dr. Gold stated that the first thing to do, in the event of a paroxysm of abnormal rhythm in which the precise mechanism cannot be ascertained, is to give the patient quinidine. May I state that I would do in such a case? First, I would endeavor to determine whether or not the patient had an abnormal rhythm. Then I would try the simple devices of carotid sinus pressure, gagging, bending the head forward between the knees and simple eyeball pressure. The next thing I would do would be to give the patient a dose of morphine. Dr. Stewart stated that he would not give morphine because if the patient had repeated attacks it might lead to addiction. In my experience with many patients I find that my worries are over after I have administered morphine. The patient with a paroxysm of auricular tachycardia is usually apprehensive and ill at ease. He is disturbed by a feeling of vigorous pounding within the chest. Not infrequently a dose of 10 or 15 mg. of morphine solves the problem before one even has had an opportunity to try out the more specific drugs to abolish the attack. The third thing I would do would be to give quinidine and in this I agree with Dr. Gold.

I was curious to know how much of a problem the abnormalities of rhythm present and so we examined the matter at Bellevue Hospital. We found that there were 181 cases of abnormal rhythms in the hospital last year. The total was broken down into the following: 122 with auricular fibrillation; eighteen with nodal rhythm;

five with supraventricular tachycardia; fourteen with auricular flutter; twelve with paroxysmal auricular tachycardia and ten with ventricular tachycardia. You will note that we had practically the same number of cases of nodal rhythm as of auricular flutter.

In connection with the comments on abolishing auricular fibrillation I am inclined to think that the danger has been overemphasized. There are two points to be considered here, namely, the danger of emboli and the fact that in some cases the restored normal rhythm does not continue. We had a patient this year in whom the fibrillation had been present for nearly two weeks; in this instance quinidine restored a normal rhythm uneventfully. This patient had no valvular disease and the heart was not markedly enlarged. I agree with Dr. Stewart's findings to the effect that patients are better off with a normal rhythm than with auricular fibrillation. Even though digitalization controls the ventricular rate in auricular fibrillation, the cardiac output is not as good as when the same patient has a normal sinus rhythm. I believe that we should try to restore a normal rhythm in these patients more often than we do. There is not sufficient time here to consider all the criteria for placing patients in the category of those in whom the attempt to restore a normal rhythm should be made.

There are figures indicating that the incidence of emboli is higher in patients with auricular fibrillation lasting a year or more than in those in whom a normal rhythm is restored. The evidence, however, is not conclusive because there may have been selection of patients, and those in whom the auricular fibrillation persisted may have been patients with a more advanced disease.

Dr. Smith referred to the recent case in which an attempt to abolish a paroxysm of ventricular tachycardia resulted in a complete auricular standstill. This occurred after about 2.5 Gm. of quinidine had been given. Yet, according to Dr. Gold, that is not an excessive amount of quinidine. It

was given in fractions at intervals of two hours.

DR. GOLD: Was that 0.6 Gm. every two hours?

DR. DEITRICK: Yes, and the patient developed a complete auricular standstill. This was temporary and was followed by restoration of a normal rhythm.

I might add one word about nodal tachycardia. I find it very difficult to control. Some of you may recall the patient here at New York Hospital last year and the difficulties encountered in his management. I wonder whether there is any better treatment than digitalis to terminate a paroxysm of nodal tachycardia. I would like to ask Dr. Gold whether quinidine has any effect on the A-V node.

DR. SMITH: Dr. Gold, maybe you are going to answer my question on procaine.

DR. GOLD: I have had no direct experience with it, but there is good experimental evidence showing that procaine has a quinidine-like action on the myocardium so that one might expect results similar to quinidine. There is the question of its dangers and that point has not been sufficiently established. Dr. Burstein published a report in the March, 1946 issue of *Anesthesiology* in which he found 30 to 70 mg. of procaine injected intravenously effective in abolishing various ectopic rhythms occurring in the course of thoracic surgery. There is the fact that these patients were anesthetized, and such doses of procaine may be safer in anesthetized individuals than in others. We need more experience in relation to the dosage of procaine. It seems to me quite worth while to pursue observations on procaine in this connection.

I think this a proper time to discuss the various comments which have been made on my opening remarks. I am glad to see that there is no disagreement with my general thesis, namely, that quinidine is the drug of choice in all of five disorders of cardiac rhythm under certain conditions. Those conditions are (1) the particular case in which a decision has been reached that normal rhythm should be restored as

quickly as possible and (2) the case in which the differential diagnosis with respect to the precise mechanism at work has not been made. The failure to establish the precise mechanism may be due to several factors; either the available facilities are not adequate, the physician is a general practitioner without sufficient experience to enable him to differentiate them or the physician is an expert in these matters, but in spite of all the measures for differential diagnosis is still unable to arrive at a precise diagnosis.

Most of the comments which appear to be in disagreement relate to a matter which I had hoped would be omitted in this conference, namely, differential diagnosis, in order to allow us time to explore more fully the items of treatment. Obviously, that would require certain assumptions, namely, that the diagnosis had been established or that a final decision concerning the diagnosis cannot be reached. Dr. Stewart indicated that the differential diagnosis between these disorders of rhythm is easy to make, and he expressed amazement that one would be unable to establish the diagnosis of a paroxysm of auricular fibrillation, auricular flutter and auricular tachycardia by clinical means. I must admit that an expert will arrive at a fairly sound hunch within a few minutes by means of the electrocardiogram and carotid sinus pressure. But I must also add that the expert who has carefully analyzed both his successes and failures in differential diagnosis will not feel particularly secure in his decision in a great many cases. Dr. Deitrick's reference to the 181 cases at Bellevue Hospital last year is of interest in this connection: In this series five cases were labeled "supraventricular tachycardia." What is the meaning of such a diagnosis? Does it not mean that in nearly 3 per cent of the cases they were unable to decide what ectopic rhythm the patient had? The term "supraventricular tachycardia" is commonly applied to an abnormal rhythm in which the electrocardiogram shows an essentially normal ventricular complex, but in which one cannot determine the nature

of the auricular activity. When one can determine it, one does not use a term which indicates merely that the pacemaker is somewhere above the ventricle, but labels the condition sinus tachycardia, auricular tachycardia, nodal tachycardia or auricular flutter. As Dr. Eggleston stated, the most rational and most effective treatment is possible only when these precise diagnoses are made. Here then is the failure to make the exact diagnosis in one of every ten cases with a regular abnormal rhythm in the hands of experts in an outstanding hospital with all the facilities for establishing the diagnosis. Consider, therefore, how much worse the situation may be in the case of the country doctor who may have no electrocardiograph, or may be less familiar with carotid sinus pressure during the taking of the electrocardiogram, as well as with the special features of the tracing which enable one to distinguish several of these disorders of rhythm.

In my opening remarks I described the treatment which is best under these conditions. The plea for establishing the mechanism of abnormal rhythm is, to be sure, quite proper. I should be the last one to recommend the treatment of disorders of cardiac rhythm without at least an attempt at a precise diagnosis, but I have had enough experience to make me aware of the rather wide gap between an attempt and success in this problem. What I wished to emphasize was the fact that in a large proportion of these cases the patient does not have to go without specific and effective treatment even though a precise diagnosis is not made.

I agree with Dr. Eggleston that many of these paroxysms of ectopic rhythm do not present urgent situations and every effort should be made to establish the precise mechanism, not only for the purpose of using the most effective method of treatment for the current attack but also to prevent repetitions. One can, of course, argue that if the situation is not urgent and the diagnosis cannot be made, one should merely sit by until the attack subsides

spontaneously. It is very likely to do so after minutes or hours or days in the majority of cases. In fact, most patients present themselves with a history of previous attacks which did subside spontaneously and that is the meaning of the term paroxysmal ectopic rhythm. We must leave it to the judgment of the physician to decide whether it is important or imperative to terminate the attack as quickly as possible. As Dr. Eggleston pointed out, these attacks sometimes give rise to a "blackout." There are other urgent problems. Some patients who never had anginal symptoms before will develop a severe attack of substernal pain radiating to both arms, wrists and back, so that one is left uncertain at the time whether an acute coronary thrombosis gave rise to the ectopic rhythm or whether the ectopic rhythm gave rise to an attack of coronary insufficiency. There are also patients in whom the circulation deteriorates as the rapid abnormal rhythm continues, and it is not long before shortness of breath, pulmonary râles and even pulmonary edema supervene. That is why I urge that the physician have a medication at his disposal for immediate use, especially in such cases, even if he remains in some doubt as to the exact nature of the ectopic rhythm, and it is for this purpose that I have recommended quinidine.

Let me come back for a moment to the matter of distinguishing the different forms of disordered rhythm. Both Dr. Pardee and Dr. Stewart indicated that it would be quite remarkable if a fellow could not distinguish clinically a paroxysm of auricular fibrillation from one of auricular tachycardia. I agree that in this case an error should be very infrequent but, on the other hand, how about the case of auricular flutter with a varying block? Can we be so sure about distinguishing this from auricular fibrillation by clinical means? There are also cases of premature contractions appearing in large numbers and at irregular intervals which are extremely difficult to distinguish from auricular fibrillation. I remember a striking experience many

years ago in the clinic of Dr. John Wyckoff. He was an expert in these matters. He then believed that the condition of frequent premature contractions was a precursor of auricular fibrillation. He showed us a patient with large numbers of premature contractions and predicted that one of these days we would find her in auricular fibrillation. Several years later he gathered a group of us at the clinic to listen to this patient and said that now she had auricular fibrillation as he had predicted she would have. Her heart beat certainly sounded like auricular fibrillation. An electrocardiogram was then taken which showed the same old condition, namely, extremely frequent auricular premature contractions. Since then I have encountered many similar problems in differential diagnosis. There is still another condition, namely, that of a paroxysm of auricular fibrillation with bundle branch block. In some the patient's normal rhythm shows a bundle branch block, and in others the bundle branch block develops as a result of the rapid rhythm of auricular fibrillation. I have rarely seen a case of this kind in which the error of calling it a ventricular tachycardia was not made. Such a tracing with a diagnosis of ventricular tachycardia was brought to my office from the Pediatric Department this very afternoon. There was no doubt of the error; it was a case of auricular fibrillation with a bundle branch block. Bundle branch block may complicate any of the supraventricular tachycardias and to distinguish these from ventricular tachycardia is a matter of first importance; for if it is a paroxysm of auricular tachycardia with bundle branch block, a large intravenous dose of a digitalis preparation may terminate the attack within a few moments. One would certainly not give digitalis to terminate a ventricular tachycardia because, first, it will fail to do so and, second, it might precipitate the disaster of ventricular fibrillation. Dr. Pardee spoke about an irregular rhythm in ventricular tachycardia as a condition much talked about but rarely seen in the electrocardiogram. That is also

my experience. I have often wondered whether most of the cases presented as ventricular tachycardia with an irregular rhythm are not in fact cases of auricular fibrillation with a bundle branch block.

Dr. Deitrick's remarks on the necessity of considering the underlying cardiac state in patients with disordered rhythms are very well taken. An acute disorder of rhythm is a dramatic event and may engage our attention to the exclusion of more important problems in the particular case. I have seen doctors preoccupied with the paroxysm of auricular tachycardia and overlook the fact that it was caused by an acute coronary thrombosis, or with the repeated attacks of auricular fibrillation and overlook an underlying Graves' disease with predominant cardiac symptoms.

Dr. Smith referred to an experience in which quinidine used in a case of ventricular tachycardia caused cardiac standstill. I have seen a few of those. They are unpleasant experiences, to say the least. The patient may stop breathing, the eyes may roll up and within a few moments there is a convulsion. Dr. Deitrick, did this patient receive 0.6 Gm. of quinidine every two hours, and if so, how many doses?

DR. SMITH: The dose was 0.4 Gm.

DR. DEITRICK: And it was given every two hours.

DR. SMITH: The total dose was 2.4 Gm. over a period of ten hours.

DR. GOLD: This patient, therefore, received six doses of 0.4 Gm. each. Very well, let us analyze the situation. We have to assume that six doses of 0.4 Gm. each, or a total of 2.4 Gm., were required in this case to terminate the ventricular tachycardia. If five doses or 2 Gm. were sufficient, I assume you would not have given the sixth dose. It is clear that you had no choice since smaller doses than those which you used would have failed to abolish the ventricular tachycardia. There are animal experiments which show that a physiologic factor inherent in the sudden abolition of a rapid ectopic rhythm may cause cardiac standstill, for other pacemakers in the heart are

frequently suppressed during the period of a rapid ectopic rhythm. The duration of the arrest varies greatly from case to case; and if it lasts as long as ten or fifteen seconds, the patient may have an asphyxial convulsion. This phenomenon does not occur only when quinidine terminates an ectopic rhythm, for it is seen when carotid sinus pressure causes A-V block in auricular flutter or terminates a paroxysm of auricular tachycardia. Although it may be that quinidine contributes to the delay in the resumption of a rhythmic discharge, the hazard of cardiac standstill is always there in the abrupt termination of a rapid ectopic rhythm, regardless of the method by which this is accomplished. Is there any way of reducing this hazard? Yes, there is. When I use quinidine in an attack of ventricular tachycardia, I do not aim to abolish the abnormal rhythm by the direct action of the drug although it may take place before anything can be done about it. I aim to slow the tachycardia to a rate which may be permitted to continue for a protracted period without impairing the circulation, for example, from an initial rate of 200 per minute to 120 or 110 per minute. When the heart functions for some time at these slower rates, the other pacemakers recover and become ready to take over promptly when the ectopic rhythm is abolished, without the delay which may give rise to a convulsion when a very rapid rhythm is brought to an end abruptly. In treating patients with ventricular tachycardia in whom I have reduced the rate from 180 or so to about 120 and then examined the electrocardiogram, I have often thanked my stars that I had not given enough quinidine to abolish the abnormal rhythm, for the tracing showed a slow idioventricular rhythm without any P waves. Had the ectopic rhythm been abolished abruptly at that point, the heart would have been left without a pacemaker, and the patient would have experienced the same reaction you encountered in the case you described. After hours or a day or so, with this slower

ectopic rhythm, a supraventricular pacemaker revives as shown by the appearance of P waves in the tracing and additional doses of quinidine may then be used safely to restore a normal rhythm in the event it does not take place spontaneously. My advice, therefore, in the treatment of ventricular tachycardia is to give 0.4 or 0.6 Gm. of quinidine every two or three hours, count the rate before each dose, continue this until the rate declines to about 120 or 110 per minute and then interrupt medication to see whether the normal rhythm will not reappear under these conditions. An electrocardiogram should be taken when the slower rates are present in order to determine whether auricular activity is in evidence and, if it is, additional doses should be given to restore normal rhythm, provided it is not already there. Large doses of quinidine act like atropine to speed up the sinus rate, and these rapid rates may lead one to assume that the ventricular tachycardia is still present unless a check is made with the electrocardiogram. There is much more to the expert management of an attack of ventricular tachycardia, but this plan avoids one of the major sources of risk.

DR. SMITH: Dr. Stewart, are there any comments you would like to make in relation to Dr. Gold's remarks? Perhaps you might wish to say something about the treatment of the patient with ventricular tachycardia who fails to respond to quinidine, and what to do for ventricular tachycardia that sometimes occurs as the result of digitalis poisoning.

DR. STEWART: Supraventricular tachycardia with bundle branch block has been reported in the literature. I do not know how many such cases there are, but they are so rare that the confusion of this condition with ventricular tachycardia is not likely to be a source of any considerable trouble.

In regard to the use of large doses of quinidine, one should bear in mind the danger of so poisoning the heart as to

suppress the sinus node. In such a case if the ventricular tachycardia is terminated the outcome may be fatal.

I might mention my experiences with cases of pericardiectomy for constrictive pericarditis which was performed by Dr. Heuer and Dr. Andrus. Frequent electrocardiograms were taken during the procedure and paroxysms of abnormal rhythm were often seen as the result of mechanical stimulation, but they ceased immediately when the surgeon gave the heart a rest.

Many of you will recall the patient here in New York Hospital who had a variety of abnormal rhythms. The attacks of nodal tachycardia were the most difficult to control in this case. In the several years of observation of this patient, during which she showed various abnormal rhythms, it sometimes seemed that digitalis was effective in preventing attacks over a long period of time and sometimes quinidine in maintenance doses seemed to prevent the paroxysms.

When a patient receives quinidine daily over long periods to prevent recurrences of paroxysms of tachycardia, an electrocardiogram should be taken from time to time to find out whether there is any widening of the QRS. This, I believe, is the only evidence of quinidine poisoning which one might be able to discover early.

DR. SMITH: I still should like to have an answer to my question on the treatment of ventricular tachycardia which fails to respond to quinidine, and the question on what to do for ventricular tachycardia which occurs in digitalis poisoning.

DR. STEWART: Quinidine rarely fails to abolish ventricular tachycardia when the drug is used in adequate amounts. If it is urgent to stop the ventricular tachycardia, for instance, in the patient with a recent coronary occlusion, it is my practice to start quinidine at once without delaying to test for idiosyncrasy to the drug. I give 0.4 Gm. and repeat this every four hours. I do not give it at intervals of two hours. In most cases the abnormal rhythm is abolished with total doses up to 2.4 Gm. on

the first day. If this proves insufficient, the dose may be increased by 0.4 Gm. the next day, and again by still another 0.4 Gm. on the third day. One should carefully watch for toxic effects.

In the group of patients who have been digitalized, mentioned by Dr. Smith, ventricular premature contractions may or may not be present; and then if quinidine is given, many ventricular premature contractions may be produced. There are reports in the literature to the effect that quinidine and digitalis together caused ventricular tachycardia, the beats arising alternately from the two ventricles. Most of these terminated fatally. There is really not much that one can do in such cases. If quinidine is continued, ventricular fibrillation may ensue and this is usually fatal. It is well to discontinue both drugs. Procaine may find a place in the treatment of this toxic effect.

DR. EGGLESTON: May I make a remark on the paroxysms of auricular fibrillation which occur in thyrotoxic patients? I have not found anything which controls these paroxysms except therapy for the correction of the hyperthyroidism, namely, iodine, thiouracil and related compounds, or surgery. Neither quinidine nor digitalis is effective in preventing the paroxysms of auricular fibrillation until the hyperthyroidism has been brought under control.

DR. GOLD: I should also like to make a few supplementary remarks at this point. Dr. Stewart stated that bundle branch block so rarely complicates a supraventricular tachycardia or a paroxysm of auricular fibrillation as to present little or no problem in differentiating these from ventricular tachycardia. I encounter that problem not at all infrequently, and I wonder whether the view that it is a rarity does not arise from the very fact that the problem is not commonly considered and an erroneous diagnosis of ventricular tachycardia is made. As I have already mentioned, most of these cases which I have seen were erroneously labeled ventricular tachycardia.

A further word on the dosage of quinidine seems to me worth while. Suppression of the sinus node during the use of this drug in ventricular tachycardia or in the case of any other ectopic rhythm for that matter is not necessarily the result of improper dosage. One cannot say that in a particular case the ventricular tachycardia would necessarily have been abolished without the auricular standstill if smaller doses had been used, for in some of these cases, as the drug is continued, the electrocardiogram may reveal a marked slowing of the idioventricular rhythm from, let us say, 200 to 120 a minute; but even in the tracing showing the slow rate, the mechanism may still be that of ventricular tachycardia without P waves as evidence of auricular standstill. This simply means that in some cases of ventricular tachycardia the level of quinidine action necessary to abolish the idioventricular rhythm is sufficient to abolish the activity of the auricles; and that if smaller doses were given, the auricular activity would not be suppressed, but then also the ventricular tachycardia would not be abolished. It is simply a matter of good fortune that in the majority of cases sufficient differential in the sensitivity of the two structures to quinidine exists, so that it is possible to arrest the idioventricular pacemaker without inactivating the sinus node. The method I described for controlling ventricular tachycardia helps to insure against suppressing both auricular and ventricular activity at the same time by quinidine.

There is another point about quinidine dosage and the likelihood of successful control of an ectopic rhythm. A large proportion of the failures to abolish an abnormal rhythm by means of quinidine is due to inadequate dosage. If we pursue the plan of giving a dose of 0.4 or 0.6 Gm. at intervals of between two and four hours and continue that system until either the ectopic rhythm is brought under control or minor toxic effects appear, such as disturbing symptoms of cinchonism, vomiting or diarrhea, the number of failures will be greatly

reduced. In the vast majority of cases which have come to my attention as failures, the drug was simply discontinued after a period of arbitrary dosage unrelated to either therapeutic or toxic effects.

Dr. Stewart referred to the widening of the QRS wave as evidence of quinidine toxicity and stressed the need of an electrocardiogram taken from time to time, which might show this effect, in patients who receive quinidine daily over long periods. I believe this is a useful device for avoiding more serious poisoning. We studied this phenomenon several years ago and found that daily doses of about 2 Gm. may prolong the QRS time by about 20 or 25 per cent. Some patients are much less sensitive and larger doses may be given before this effect occurs. It does not seem wise to increase the dose of quinidine beyond that which prolongs the QRS time by 25 per cent above the control for that person although it is possible that one can produce even greater QRS prolongation without serious consequences. In this connection perhaps we should call attention to the fact that if a patient receives a fixed daily dose for about five days and at the end does not show this effect, it is not necessary to take any more electrocardiograms later. This is so because quinidine cumulation, like that of many other drugs, is a self-limiting process, and all cumulation of quinidine that is going to take place with a fixed daily dose occurs during the first four or five days. Therefore, if a particular effect has not taken place by that time, there is little likelihood of its occurring later.

In relation to Dr. Smith's question as to how to treat ventricular tachycardia which is not controlled by quinidine even when the drug has been given to the point of toxic effects, the earlier comment by Dr. Pardec may be recalled. An intravenous dose of magnesium sulfate, 10 or 15 cc. of a 10 per cent solution, is sometimes quite effective. An intravenous dose of procaine might also be tried, but with this I have had no experience.

Dr. Smith has also asked about ventricular tachycardia due to digitalis poisoning. I would suggest that no attempt be made to terminate this by any drug. In experiments on animals, which were published several years ago, we found quinidine very effective in terminating the ventricular tachycardia induced by digitalis. It was usually a fleeting effect and seemed to be a result not only of direct action on the ventricle but also a result of the fact that the sinus node was so much accelerated as to make the auricular activity faster than the idioventricular activity. A source of serious danger appeared in these experiments, namely, the fact that ventricular arrest often occurred due to the fact that the dose of digitalis which had poisoned the heart sufficiently to induce ventricular tachycardia had also produced complete block by its direct action on the A-V node. Since the existence of such a block is masked in the electrocardiogram showing a ventricular tachycardia, it seems to me wiser to refrain from using quinidine or any other drug to abolish the ventricular tachycardia caused by digitalis poisoning. It is probably the lesser of the two evils to allow the ventricular tachycardia to continue until it disappears spontaneously as the elimination of the digitalis takes place.

DR. N. T. KURT: In regard to the dose of mecloyl I was surprised to hear that the range of doses for younger people was lower than that for older people. I would have expected the reverse since older people are so much more likely to have coronary disease which is sometimes stated to be a contraindication to the use of mecloyl. I recall an experience in which a man, fifty years of age, developed a paroxysm of auricular tachycardia for which I used mecloyl. He had never complained of angina of effort, but after a dose of 50 mg. subcutaneously and while the attack subsided, he developed a terrifying attack of substernal pain.

DR. WALTER MODELL: It has been stated here that digitalis is effective in abolishing a paroxysm of auricular tachycardia and that the drug may also be continued to

prevent recurrences. I believe I once heard Dr. Gold mention some tricks for increasing the efficacy of digitalis in a paroxysm of auricular tachycardia and auricular flutter.

DR. SMITH: What are they?

DR. GOLD: In a paroxysm of auricular tachycardia one is likely to use digitalis only after the various devices which have already been described have failed. The point I have in mind is based on the fact that digitalis increases the sensitivity of the heart to carotid sinus pressure. Inject 0.3 mg. ouabain intravenously and wait about thirty minutes. Now carotid sinus pressure may terminate the attack abruptly. If the dose of ouabain turns out to be too small for the particular patient, the tachycardia may return within a few minutes. In that event one may safely repeat the dose of ouabain and the carotid sinus pressure. This technic frequently makes it possible to abolish a paroxysm of auricular tachycardia with smaller amounts of digitalis. Any of the intravenous injectable digitalis preparations may be used for this purpose although the more rapidly acting ones are more practical.

There are several ways of applying digitalis in a case of auricular flutter. In many instances there is little more to it than the fact that a normal rhythm appears after very large doses of digitalis have been given. In others, however, the digitalis will convert the flutter into fibrillation, and the fibrillation may persist as long as the digitalis is continued. In these patients the restoration of a normal rhythm takes place only after the digitalis is discontinued. Here also a rapidly eliminated digitalis preparation is the most practical.

DR. SMITH: Dr. Pardee, could we have some remarks from you on the subject of heart block and the Adams-Stokes attacks?

DR. PARDEE: In patients subject to Adams-Stokes attacks, the diagnosis of the particular mechanism is very important. The mechanism is often one of prolonged A-V conduction in which there is a fleeting period of complete dissociation. This gives rise to spells of transient giddiness, usually

without convulsions, because the normal conduction soon reappears.

Among patients who have complete heart block and who develop more severe attacks of syncope there are two mechanisms. In one type the syncope is due to ventricular arrest. These patients usually have an irregular ventricular rhythm with a slow rate of 20 or so. In the second type the syncope may be associated with ventricular fibrillation. These patients may have a somewhat higher ventricular rate but the rhythm is apt to be interrupted by premature contractions. Such a finding between the attacks should make one suspect that the convulsive seizures are probably due to ventricular fibrillation. Digitalis and ephedrine to increase the rhythmicity of the myocardium are often helpful in the types of heart block in which the syncope is due to ventricular arrest, but they seem to aggravate the type in which ventricular fibrillation occurs. Sedatives, such as bromides or phenobarbital, seem to be helpful in the patients in whom convulsions occur as the result of ventricular fibrillation.

At this point it should be mentioned also that there is no contraindication to using digitalis in the patient with chronic heart block if heart failure is present.

DR. MODELL: How would you treat congestive failure which might develop during a paroxysm of one of the ectopic rhythms? Assume that you had not yet found the proper drug or combination of drugs to abolish the paroxysm. I should also like to know whether it is not true that the control of the failure sometimes abolishes the ectopic rhythm.

DR. SMITH: Dr. Deitrick, will you try your hand at this?

DR. DEITRICK: If it happens to be a supra-ventricular tachycardia, it is fortunate because one can then use digitalis freely. In the case of ventricular tachycardia I do not have the courage to digitalize even in the presence of congestive failure. I try to stop the paroxysm of tachycardia as quickly as possible.

DR. MODELL: How about using a mercurial diuretic?

DR. DEITRICK: I would use it but I do not think that is the answer to the problem. One simply has to abolish the ectopic rhythm before the function of the heart can be improved materially.

DR. PARDEE: I know of two patients with ventricular tachycardia in whom failure developed and who were treated with digitalis. Both of them died.

DR. SMITH: Was quinidine used in these cases?

DR. PARDEE: Quinidine had been used but was ineffectual. Everything we tried failed.

DR. SMITH: I take it that the last thing you tried was digitalis.

DR. PARDEE: Yes. The ventricular tachycardia was somewhat slowed by quinidine but it was not possible to abolish the rhythm. When the patient developed frank signs of failure, he was digitalized.

DR. GOLD: I think Dr. Modell's question merits more attention. An intensive course of dehydration by the use of milk as the sole diet, liberal water intake and a daily intramuscular injection of 2 cc. of a mercurial diuretic should go a long way in helping to control the congestive failure which develops during a paroxysm of a rapid ectopic rhythm. I am inclined to believe that these measures are more effective than digitalis in such cases, so that one does not need to worry too much over the fact that digitalis is omitted.

There is an important point in his second question also. Paroxysms of ectopic rhythm are sometimes the first manifestations of a failing heart. There may be paroxysms of auricular fibrillation, auricular tachycardia, ventricular tachycardia and others. An effective course of dehydration by means of salt restriction and frequent doses of the mercurial diuretic sufficient to reduce the patient to his "dry weight" is often successful in abolishing attacks of ectopic rhythm and preventing their recurrence.

DR. MODELL: I was interested in the comment on the matter of having atropine

on hand in the event that carotid sinus pressure caused cardiac asystole. It is not quite clear to me what purpose it would serve since if there is asystole there is no circulation, and even if the atropine were injected into the vein or directly into a chamber of the heart, there would be no means of transport to the site of its action. I know that carotid pressure may produce cardiac standstill of duration that is very disquieting; it may last long enough to give rise to an asphyxial convulsion, but I believe it is a fact that escape from vagal control is the rule and that disaster from the use of carotid pressure is extraordinarily rare if indeed it occurs at all.

VISITOR: I would like to ask Dr. Gold what he does for a paroxysm of sinus tachycardia.

DR. GOLD: This is the most common form of tachycardia and we have no specific treatment for it.

DR. SMITH: How about removing the cause?

DR. GOLD: That is what we try to do but we cannot boast of our success. I assume that we may omit from consideration the patient with Graves' disease or with fever in whom sinus tachycardia occurs. The patients who complain of attacks of rapid heart action and in whom these turn out to be paroxysms of sinus tachycardia are individuals with autonomic imbalance, disturbed psychic states, tension states and the instability of the menopause. We have no drugs which act directly to produce persistent slowing of the sinus rhythm. We try to treat the nervous state. We sometimes use sedatives or suggestion or whatever else seems indicated by the various and sundry problems presented by the particular individual. They may improve but, on the whole, the therapeutic results are not particularly striking.

DR. SMITH: Are there any further questions?

VISITOR: Suppose you were faced with the problem of a patient who had just suffered a myocardial infarction which precipitated auricular fibrillation with a ventricular rate

of 160 a minute. What would you do? Would you try to abolish the fibrillation or merely try to slow the ventricular rate?

DR. SMITH: Would you answer that, Dr. Eggleston?

DR. EGGLESTON: I have been confronted with that problem on several occasions. I do not try to restore the normal rhythm. Very often the auricular fibrillation which occurs in association with an acute coronary thrombosis is of short duration. It has been my practice to resort to digitalis to slow the ventricular rate and to relieve or prevent congestive failure. I do not believe there is any contraindication to the use of digitalis even in fresh infarction.

SUMMARY

DR. GOLD: The treatment of disorders of cardiac rhythm was explored in this conference. This was a very large undertaking. There are several types of disorders of rhythm; there are various devices for distinguishing one from another. It is important to do so for there are significant differences in the treatment of each, and the most successful results depend on the use of measures specifically suited to the particular problem. A special conference could be profitably devoted to any one disorder of rhythm.

There has been no attempt to exhaust the subject, but many points of practical interest have been brought out in the account of experience and opinion by the various participants. Many of the details cannot be satisfactorily summarized without repeating the conference. The following disorders of rhythm received attention: premature contractions, auricular and nodal tachycardia, auricular flutter, auricular fibrillation, ventricular tachycardia and heart block. There was some discussion of the management of congestive failure in the course of a paroxysm of abnormal rhythm and the problem of ectopic rhythms occurring in the hyperthyroid state. It was pointed out that three distinct problems prevail in cases of disordered rhythm, namely, those in whom the disordered rhythm is a chronic phenomenon

and is to be allowed to continue, those in whom an acute paroxysm needs to be terminated and those in whom the problem is essentially one of preventing recurrences. Means for differential diagnosis were described, namely, certain clinical features, the electrocardiogram, carotid sinus pressure and various devices exerting similar effects.

The application of several drugs was discussed in some detail, such as quinidine, digitalis, magnesium sulfate, procaine, mecholyl, ipecac, ephedrine, morphine and other sedatives. In a patient with a paroxysm of rapid heart action which does not appear to be damaging the circulation unduly, there are some who prefer to give a dose of morphine to make the patient more comfortable and let the problem rest until the abnormal rhythm ceases spontaneously. Digitalis appears to be the drug of choice for the paroxysm of auricular and nodal tachycardia. While mecholyl is very effective, it is so apt to produce disturbing symptoms that it is best to keep it in reserve for use when other measures fail. Quinidine is the standard remedy for an attack of ventricular tachycardia; and when for one reason or another it proves inadequate, an intravenous injection of magnesium sulfate is sometimes effective. There are risks

involved in the use of all these drugs to abolish a paroxysm of abnormal rhythm, and technics were described for reducing the hazards to a minimum.

Attention was called to the fact that there are many situations in which a differential diagnosis among the disorders of rhythm is difficult or impossible to make, but that even under those conditions, a specific form of therapy is still available; for quinidine is highly effective against five of the more common disorders of rhythm: premature contractions, paroxysmal auricular tachycardia, auricular flutter, auricular fibrillation and ventricular tachycardia. Strong emphasis was placed, however, on the desirability for making every effort to establish the precise mechanism before treatment is started, for only then is the most rational and effective plan of therapy possible.

Finally, the point was made that one should always bear in mind the underlying state of the heart in which a rapid ectopic rhythm has suddenly appeared. The abnormal rhythm is a dramatic event and may engage the attention of the examiner to the exclusion of other factors of far greater importance than the abnormal rhythm, such as Graves' disease or an acute coronary thrombosis.

Progressive Congestive Heart Failure with Peripheral Vascular Collapse*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. I., (B. H. History No. 140,836), a forty-six year old married negroess, entered the Barnes Hospital for the first time on November 4, 1946, complaining of shortness of breath and swelling of the abdomen and legs. The family history was of interest in that the patient's mother died late in life from "leakage of the heart." The patient was one of nineteen children, eight of whom were living. No details were known regarding the causes of death of the other siblings.

Prior to the age of twenty-two the patient had recurrent attacks of chills and fever which had been diagnosed as malaria but subsequently she had very few such episodes. She did not recall ever having scarlet fever or rheumatic fever but stated that she had always been subject to "head colds," and for the ten years prior to admission she had occasional paroxysms of wheezing which lasted two to three hours; these occurred particularly in damp weather. The patient had no other symptoms suggestive of allergic disease. Throughout most of her adult years she had recurrent nose bleeds. When she was eighteen she was told that the epistaxes were due to high blood pressure and a similar comment was made to her by a physician four years before entry into the hospital. Over a period of some thirty years the patient had severe headaches every few months which lasted three to four days.

Four years before admission she was told that she had "bad blood," and was given

a total of ten intramuscular injections at weekly intervals. She denied any local lesion or eruption in earlier life suggestive of syphilis. She had one child; two other pregnancies terminated spontaneously at four months. For many years she had weighed between 220 and 230 pounds. Until the age of thirty she had worked as a cotton picker but subsequently her activities were those of a housewife. Her habits were not remarkable.

Three years before admission the patient for the first time noted swelling of the ankles which was more pronounced in the evening and which disappeared overnight. She was free of other signs and symptoms until one year later when her abdomen became distended; soon after she noted shortness of breath on moderate exertion. She consulted a physician who prescribed "one green pill daily." She took the pills for two weeks after which the ankle swelling disappeared and did not recur for several months. When the swelling again became apparent, she resumed taking the green pills and once again noted improvement. The program of self-medication was continued for about one year but during this period the patient's abdomen gradually became larger.

One year before admission she consulted another physician who gave her an injection, subsequent to which she passed a large amount of urine and the swelling in her abdomen quickly subsided. When her abdomen again became distended after several months, she consulted the physician

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who repeated the injection and once more an apparently satisfactory diuresis resulted. Four months before entry she was seen at another hospital at which a paracentesis was performed. She was told to follow a salt-poor diet and was given medication, the nature of which was not known. Her symptoms improved a great deal following institution of this regimen and she continued to do well until a neighbor advised her that a teaspoonful of salt a day would be very beneficial. The patient followed this suggestion and became markedly edematous once more. Dyspnea on exertion became extreme and she was particularly short of breath at night. She stated that for several years prior to entry she had occasional short fleeting pains over her chest which came on with exertion and were relieved by rest. No further details in regard to this complaint could be elicited, however, and the patient's only additional complaint was that she occasionally suffered palpitation which would "shake my whole body."

Physical examination at the time of admission revealed the patient's temperature to be 36.8°C., pulse 100, respirations 32 and blood pressure 130/85. The patient was an obese negress who was acutely ill and obviously uncomfortable. Dyspnea was so marked that she had great difficulty in speaking. The respirations were shallow but cyanosis was not present. The pupils were round, regular and equal and reacted to light and accommodation. The sclerae were not icteric. Examination of the fundi revealed no hemorrhages or exudates but the arterioles were markedly tortuous. No abnormal findings were noted in the upper respiratory tract. The trachea was in the midline. The neck veins were markedly engorged. The upper anterior chest was prominent and heaving pulsations could be seen over that area. The lungs were resonant to percussion throughout and breath sounds were well heard. An occasional r  le was present at the lung bases. The cardiac impulse was heaving over the entire precordium. No thrills were palpated. The left border of cardiac dullness was

14 cm. from the mid-sternal line in the fifth interspace and right border dullness was 8 cm. from the sternum in the fourth interspace. The sounds were loud; a gallop rhythm was audible at the apex and occasional extrasystoles were heard. The first sound was normal in intensity; it was followed by a grade III systolic murmur which was well transmitted to the axilla and was heard also to the right of the sternum. No diastolic murmurs were described and P₂ was not accentuated. The abdomen was enormously distended and the signs of ascites were striking. Adequate palpation was not possible because of the huge amount of peritoneal fluid. Pelvic and rectal examination were both normal. There was 4 plus pitting edema extending above the knees and marked sacral edema was likewise present. The neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 4,160,000; hemoglobin, 12 Gm.; white cells, 7,200; differential count: eosinophiles, 2 per cent; juvenile forms, 2 per cent; stab forms, 2 per cent; segmented forms, 65 per cent; lymphocytes, 25 per cent; monocytes, 4 per cent. Urinalysis: albumin, trace; sediment, occasional granular cast. Blood Kahn test: positive (20 units). Stool examination: guaiac negative. Blood chemistry: non-protein nitrogen, 15 mg. per cent; total protein, 4.2 Gm. per cent; albumin, 2.5 Gm. per cent; globulin, 1.7 Gm. per cent; icterus index, 18 units; cephalin-cholesterol flocculation test, negative; alkaline phosphatase, 3 Bodansky units. Venous pressure: 330 mm. of saline. Circulation time (decholin): 75 seconds. Roentgenogram of the chest: "There is marked enlargement of the cardiac shadow both to the right and left. The aorta is lengthened. The lungs appear clear." Electrocardiogram: P-R interval, .24 seconds; T waves, low upright in lead I; premature ventricular contractions.

Soon after admission an abdominal paracentesis was performed and 10 liters of slightly turbid, straw-colored fluid were removed. On examination the specific

gravity of the fluid was 1.015 and it contained 195 mononuclear cells. Following paracentesis, re-examination of the abdomen revealed the liver edge to be 10 cm. below the right costal margin and pulsation of the liver was described. Fluoroscopic examination of the chest revealed the heart to be globular in shape with enlargement of both the left and right sides. The aortic shadow was small. The pulmonary conus did not seem to be enlarged.

The patient was given 1.2 mg. of digitoxin orally and on the following day the gallop rhythm disappeared. Then for the first time a long, loud, mid-diastolic rumble was heard at the apex; the systolic murmur previously described was still present. The diastolic murmur persisted thereafter. The patient was given ammonium chloride and mercupurin and her improvement was striking. During the first week of her hospital stay she lost 53 pounds. The liver became smaller in size and no longer pulsated. The venous pressure fell to 78 mm. of saline and the decholin circulation time decreased to 28 seconds. The cardiac rhythm which had been regular became grossly irregular and a subsequent electrocardiogram showed auricular fibrillation. Because of the positive serologic test for syphilis, a lumbar puncture was performed; the spinal fluid was entirely normal. The patient left the hospital on November 16, 1946, to be followed in the medical clinic. She was advised to follow a salt-free diet and to continue taking digitoxin.

She did quite well for about one month but then ankle edema, abdominal swelling and dyspnea began to reappear. Although she had apparently adhered to the therapeutic regimen quite closely and was faithful in her clinic attendance, her condition became progressively worse and on February 23, 1947, she was re-admitted to the Barnes Hospital. In the week before admission she had developed a loose, productive cough.

Physical examination at the time of entry revealed the temperature to be 37.2°C., pulse 90, respirations 26 and blood

pressure 170/80. The following changes from those previously recorded were described: The patient was slightly dyspneic and orthopneic. Her sclerae were moderately icteric and the eyeground vessels showed tortuosity and narrowing. There was marked distention of the neck veins and of the veins of the forehead. Examination of the lungs revealed fine, moist râles at both bases. The left border dullness was noted 11 cm. from the mid-sternal line in the fifth interspace. The rhythm was totally irregular with long periods of coupling. A harsh, grade iv, high-pitched, systolic murmur was heard in the mitral area and a similar murmur could be heard over the tricuspid area. The mid-diastolic apical rumble was audible but seemed distant. The abdomen was distended with evidence of a moderate amount of fluid. A midline diasthesis of the rectus muscles permitted a 4 by 4 cm. herniation of the abdominal contents. The hernia was tender to palpation and painful even when not touched. The liver was felt 16 cm. below the costal margin in the midline. It was markedly tender and systolic pulsations were easily felt. Four plus brawny pitting edema in both lower extremities extended up to the sacrum.

The laboratory findings were as follows: Blood count: normal throughout. Urinalysis: albumin, 3 plus; sediment, occasional granular cast. Blood Kahn test: positive (4 units). Blood chemistry: non-protein nitrogen, 17 mg. per cent; total protein, 7.7 Gm. per cent; albumin, 4.0 Gm. per cent; globulin, 3.7 Gm. per cent; icterus index, 18 units; cephalin-cholesterol flocculation test, 2 plus; CO₂ combining power, 47.7 volumes per cent; chloride, 100 mEq./L.; bromsulfalein dye retention, 40 per cent in 30 minutes. Venous pressure: 350 mm. of saline. Circulation time (decholin): 28 seconds. Roentgenograms of the chest: "The findings are not unlike those previously noted except that the left border of the heart is not as sharply outlined and there appears to be a diffuse homogeneous shadow obliterating the left costophrenic angle which does not have the appearance

of fluid. A flat film of the abdomen shows a calcified mass approximately 5.7 cm. in diameter in the left side of the pelvis, presumably a calcified myoma." Electrocardiogram: Auricular fibrillation; abnormal form of ventricular complex; full intraventricular conduction time and left axis deviation. Phonocardiogram was interpreted as showing no evidence of the murmur of tricuspid stenosis although there was some suggestion of a tricuspid systolic murmur. Special studies of the liver pulsations suggested that they were due to the marked impact of the heart in systole.

On admission the patient was fluoroscoped and the trachea was found to be pushed slightly to the right. The heart was greatly enlarged to both right and left, the left ventricle being particularly huge. The pulmonary conus was quite prominent. A barium swallow revealed deviation of the esophagus backward and to the right in the region of the cardiac base.

The patient's pain at the site of the abdominal hernia became more severe. She was given morphine; the hernia was then reduced easily by manipulation. Therapeutic measures were instituted which included a salt-free diet and 0.2 mg. of digitoxin and 12 Gm. of ammonium chloride daily. Mercupurin was given intravenously at frequent intervals. Once again the patient responded well and by the fourth day had lost 21 pounds. The râles in her chest disappeared and she was more comfortable. She was allowed to be up and about and aside from complaining of cramps in the right calf muscle she was free of symptoms. Examination of both legs showed no abnormalities. On the morning of the tenth hospital day the patient complained of nausea and weakness and she began to perspire. When questioned by a house officer, she also complained of substernal pain. Examination of the heart revealed the findings to be unchanged. Her blood pressure at the time was 180/120. That afternoon the patient developed severe lower abdominal pain and definite tender-

ness was noted on palpation over that area. The skin was cold and perspiration was profuse. The patient vomited approximately 1 liter of undigested material and her blood pressure gradually fell to 110/82. The heart sounds became poorer in quality and a protodiastolic gallop rhythm became audible. The abdominal tenderness increased progressively and an electrocardiogram was suggestive but not conclusive of myocardial infarction. Two hundred fifty cc. of pooled plasma were given slowly but the patient failed to improve. She continued to perspire profusely, became unresponsive, stuporous and finally comatose and expired within a few hours of the onset of abdominal pain. During the last twenty-four hours in the hospital her temperature, which had been at levels just above normal, rose to 39.6°C. Death occurred on March 5, 1947.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: I believe we are faced with two major questions: the first in regard to the type of heart disease with which the patient was afflicted and the second, the cause and nature of the terminal episode. Dr. Massie, will you open the discussion by telling us what type of heart disease you believe this patient had?

DR. EDWARD MASSIE: Chiefly on the basis of the auscultatory findings, it seems quite likely that the patient had rheumatic heart disease. She had the classical murmurs of mitral stenosis and insufficiency and even in the absence of a typical history I believe the diagnosis is still obvious. It is well worth pointing out that she had numerous nose bleeds in earlier life which is at least consistent with rheumatic infection.

DR. ALEXANDER: She was told at the age of eighteen that she had hypertension and that the elevated blood pressure was the cause of her epistaxes.

DR. MASSIE: I think that explanation is quite unlikely. It would be unusual for a patient to have epistaxes on the basis of hypertension at the age of eighteen and live to the age of forty-seven.

DR. ALEXANDER: Is death at the age of forty-seven in keeping with the course of rheumatic heart disease?

DR. MASSIE: Yes, it certainly is.

DR. ALEXANDER: Does the description of the heart size and the contour seem consistent with the diagnosis of rheumatic heart disease?

DR. MASSIE: Yes, I think the findings are quite consistent with rheumatic valvular deformities, more so really than with hypertension or coronary artery disease.

DR. ALEXANDER: Why should the left ventricle have become so large?

DR. MASSIE: I believe the description states that the heart was enlarged both to the left and the right and that the right-sided enlargement was quite striking. I am impressed by the latter fact for I believe it favors the diagnosis of rheumatic heart disease. In hypertension left ventricular enlargement is common but the right side does not increase to such a degree.

DR. ALEXANDER: Dr. Bottom, do you care to comment?

DR. DONALD S. BOTTOM: I think that globular contour of the heart as seen in the x-ray films was quite in keeping with the diagnosis of mitral valvular disease.

DR. ALEXANDER: In other words, the evidence both from physical examination and from x-ray examination certainly favors the diagnosis of rheumatic heart disease. Furthermore, the patient was given a barium swallow and the esophagus was noted to be deviated. What interpretation is given to that finding, Dr. Glaser?

DR. ROBERT J. GLASER: It is indicative of left auricular enlargement resulting from mitral stenosis.

DR. ALEXANDER: Dr. Smith, would you care to defend the diagnosis of hypertensive cardiovascular disease?

DR. JOHN R. SMITH: No, I would not. In the first place, the patient's blood pressure was not significantly elevated. Secondly, as Dr. Massie has stated, the rather typical murmurs and the heart size are more in keeping with rheumatic heart disease than with hypertensive cardiovascular disease.

DR. ALEXANDER: She had been told twice in her life, once at the age of eighteen and again approximately at the age of forty-three, that she had hypertension. The eyeground changes were somewhat suggestive of hypertension, particularly on her second admission, and the radiologist told us that she had a lengthened aorta. Terminally, the electrocardiogram suggested coronary abnormalities. What importance do you attach to these data?

DR. SMITH: I believe these vascular changes were probably due to arteriosclerosis and I am unable to support the diagnosis of hypertensive cardiovascular disease.

DR. ALEXANDER: Dr. Scott, do you think the patient possibly had syphilitic heart disease?

DR. VIRGIL C. SCOTT: No, I see no evidence for that diagnosis.

DR. HENRY A. SCHROEDER: I believe it is likely that this patient had hypertensive cardiovascular disease. Aside from the murmurs all the findings are consistent. She had a history of hypertension and lack of elevation of the blood pressure is not uncommon in the presence of cardiac insufficiency.

DR. ALEXANDER: Her blood pressure was recorded twice daily during her first admission and all the values were well within normal limits. On the second admission the first value recorded was 170/80. Other readings, in general, were within normal limits.

DR. SCHROEDER: I still do not believe that the level of blood pressure in the presence of cardiac failure is significant one way or another in regard to the presence or absence of hypertensive cardiovascular disease. Furthermore, the description of the retinal vessels, particularly on the second admission, is consistent with hypertension. In regard to the x-ray findings it seems likely to me that the contour was distorted by cardiac dilatation and probably by enlargement of the auricles which one would expect in right-sided heart failure. I think murmurs such as were described

here may occasionally be seen in the presence of cardiac insufficiency and although they favor rheumatic heart disease I do not think that they definitely substantiate that diagnosis.

A STUDENT: Is auricular fibrillation more compatible with one diagnosis than the other?

DR. ALEXANDER: Auricular fibrillation may occur with either of the types of heart disease we are discussing.

DR. MASSIE: Auricular fibrillation makes it more difficult to hear mitral diastolic murmurs. In view of the fact that the combination of hypertensive and rheumatic heart disease is not uncommon I believe it is possible that the patient had both. If she had both, all the findings could easily be explained.

DR. ALEXANDER: Dr. Smith, do you believe the patient had a tricuspid lesion?

DR. SMITH: She certainly may have had. Very large hearts may be produced by tricuspid lesions, particularly tricuspid insufficiency.

DR. ALEXANDER: That lesion, of course, would be due to rheumatic heart disease, would it not?

DR. SMITH: Yes.

DR. SCHROEDER: In the presence of marked cardiac dilatation, functional tricuspid insufficiency may develop which may be indistinguishable from that of an actual abnormality of the tricuspid valve itself.

DR. ALEXANDER: Do you believe that in this case cardiac insufficiency, on the basis of hypertensive and arteriosclerotic coronary artery disease, was of sufficient degree that the tricuspid valve was functionally involved?

DR. SCHROEDER: I have seen cases of predominantly right-sided failure in which the patient developed a high venous pressure and a pulsating liver; at autopsy no tricuspid abnormality was apparent.

DR. SMITH: In passing we should mention that chronic pericarditis may give rise to a clinical picture much like the one with which we are faced here, that is, a markedly

enlarged heart with signs of right-sided failure, high venous pressure, chronic passive congestion and cardiac cirrhosis.

DR. MASSIE: One point definitely against the diagnosis of pericarditis here is the fact that the patient's venous pressure fell to within normal limits; in pericarditis, either constrictive or adhesive, that is not usually the case for even when such patients improve their venous pressure remains at a high level.

DR. SMITH: I agree that the diagnosis of pericarditis is difficult to support when the venous pressure is not elevated but occasionally, even in the presence of pericarditis, it is not particularly high.

DR. ALEXANDER: When we speak of pericarditis we should think of two types. There may be actual constriction of the pericardium at the point where the great veins enter the heart. On the other hand, there may be chronic pericarditis consisting of mediastinal adhesions or of adhesions between the myocardium and pericardium itself with obliteration of the pericardial space. Now, if the great veins are constricted, I do not see how the venous pressure could fall, even with improvement, to the degree which was seen in this patient.

DR. MASSIE: I agree that the drop in venous pressure of the magnitude recorded here would be very surprising in pericarditis. I should like to mention further that the greatest degree of tricuspid insufficiency occurs in association with mitral stenosis because of the right ventricular enlargement and dilatation which leads to dilatation of the tricuspid valve ring.

A STUDENT: Is it possible that the patient had an interventricular septal defect with a paradoxical embolus arising in the leg vein and going to one of the mesenteric arterics?

DR. ALEXANDER: That is a very interesting suggestion which would perhaps explain the calf pain and the final abdominal episode. Dr. Massie, would you care to comment on this point?

DR. MASSIE: I think the systolic murmur is better explained on the basis of mitral insufficiency than by a septal defect and,

therefore, the only reason for bringing in that suggestion is, of course, to base the cause of death on a paradoxical embolus.

DR. GLASER: One other diagnostic possibility which should be mentioned in passing is Lutembacher's syndrome, patent foramen ovale with mitral stenosis. I believe the patient had rheumatic heart disease and not Lutembacher's syndrome, however.

DR. ALEXANDER: That is an interesting suggestion which certainly should be mentioned. I believe it is interesting that this patient had marked edema and ascites for a long period of time before she developed shortness of breath. Dr. Moore, would you care to comment?

DR. CARL V. MOORE: I think she simply had right-sided failure for several years and it was not until she developed left-sided failure that the shortness of breath, dyspnea and cough became apparent.

DR. ALEXANDER: What abnormalities would you expect to find in her liver?

DR. C. V. MOORE: I should expect to find the changes of so-called cardiac cirrhosis.

DR. ALEXANDER: Dr. Wade, do you think she had Laennec's cirrhosis?

DR. WADE: I do not see much evidence to support that diagnosis.

DR. ALEXANDER: Do you believe then that she will have cardiac cirrhosis as Dr. Moore suggests?

DR. WADE: Yes, I would think it quite likely.

DR. HAROLD A. BULGER: When in a negro patient murmurs suggestive of rheumatic heart disease are noted, the diagnosis of sickle cell anemia should always be considered.

DR. ALEXANDER: Dr. Moore, do you believe that the cardiac manifestations here may have been due to sickle cell anemia?

DR. C. V. MOORE: I believe that Dr. Bulger's suggestion is a very good one indeed, but I do not believe it holds here because the patient's blood count was repeatedly normal. If this had been sickle

cell anemia, there should have been an anemia at one time or another.

DR. ALEXANDER: Dr. Scheff, prior to the terminal episodes the patient apparently suffered great pain from an abdominal hernia which was reduced after she had been given suitable sedation. Some days later she developed signs of peripheral vascular collapse following severe lower abdominal pain. Do you think that she probably had an intestinal lesion?

DR. HAROLD SCHEFF: I think one must certainly consider an occlusion of one of the mesentery vessels, either a mesentery thrombosis or an arterial embolus.

DR. ALEXANDER: Is not an embolus to the mesenteric arteries very rare?

DR. SCHEFF: Yes, it is rare but I believe it is more frequent than mesenteric thrombosis.

DR. SCHROEDER: This patient lost 21 pounds in four days and apparently was given considerable mercurial diuretics intravenously. She complained of cramps in her calf, had nausea, weakness, perspired profusely and also noted abdominal and substernal pain. In this connection we should mention a syndrome known as hypochloremic azotemia which may cause renal shutdown and is often associated with the use of mercurial diuretics. It is probably due to loss of chloride and can be reversed by administration of salt.

DR. ALEXANDER: Would that diagnosis be substantiated at the time of autopsy?

DR. SCHROEDER: I do not think so.

DR. ALEXANDER: I believe it is a very good point. Dr. Massie, do you believe the terminal event may have been coronary occlusion? The electrocardiographic changes were said to have suggested that possibility.

DR. MASSIE: I reviewed the electrocardiograms in this case and do not think that the changes really suggested myocardial infarction. I doubt that the patient had an infarct.

DR. ALEXANDER: In summary, it appears that the cardiologists, in general, favor rheumatic heart disease with mitral and possible tricuspid involvement as the most likely diagnosis. It is also thought that the

patient will have cardiac cirrhosis; pericarditis has been mentioned in passing and a vascular accident involving one of the abdominal mesenteric vessels has been proposed as a possible cause of abdominal pain.

Clinical Diagnosis: Rheumatic heart disease with mitral insufficiency; mitral stenosis; ? tricuspid insufficiency, marked cardiac insufficiency, advanced; cardiac cirrhosis; ? mesenteric or embolic thrombosis.

PATHOLOGIC DISCUSSION

DR. PARKER R. BEAMER: External examination of the body revealed moderate pitting edema of the legs but there were no other significant findings. When the chest was opened, no fluid was present in either pleural cavity. The pericardial sac contained 15 cc. of clear yellow fluid. The heart was markedly enlarged, weighing 810 Gm. In the region of the left atrioventricular groove an irregular area of the epicardium measuring 15 by 5 cm. was covered by a thin layer of gray, friable, loosely adherent material. Elsewhere the epicardium was thickened and opaque. The wall of the right ventricle measured 6 mm. in thickness and the wall of the left ventricle 16 mm. in thickness. Throughout the myocardium there were indistinct linear foci of gray-white fibrous tissue. The endocardium lining the chambers of the heart was not unusual except for slight increase in thickness and opacity in the left atrium above the mitral ring. Similar thickening of slight degree involved the free edges of the tricuspid and mitral valves but the chordae tendineae were not unusual. Between the cusps of the pulmonary and aortic valves there were a few delicate adhesions. The ostia of the coronary arteries were widely patent and dissection revealed no significant abnormalities in the branches of either vessel. The wall of the aorta was slightly thickened and several irregular, firm, slightly raised yellow plaques were apparent on the intimal surface. Just above the aortic valve there were a few indistinct and poorly outlined continuous areas of wrinkling of the

intimal surface over firm, pearl-gray foci of thickened intima. In the subjacent media a few minute red spots were apparent.

The visceral and parietal pleural surfaces were smooth and glistening. All lobes of the lungs were slightly to moderately subcrepitant. The cut surfaces were dark red and frothy sanguineous fluid could easily be expressed. The mucous membranes of the bronchi were red and swollen. A calcified nodule 1 cm. in diameter was present in the peripheral portion of the lower lobe in the left lung and a similar focus 7 mm. in diameter was found in a tracheobronchial lymph node on the left.

The liver was slightly enlarged, weighing 1,820 Gm; its capsule was smooth and glistening. The substance cut with increased resistance and the surface was firm, mottled and slightly nodular. In some areas the architectural pattern was distinct, revealing well outlined lobules with dark red-brown central areas some of which, in turn, were partially circumscribed by indefinite yellow-brown foci. The portal areas were apparent in many instances as irregular gray-white linear foci. Scattered throughout the parenchyma, pale brown nodules up to 1 cm. in diameter were seen. These protruded slightly above the surface of the adjoining hepatic lobules.

The kidneys each weighed 180 Gm. The capsules stripped easily, revealing finely granular surfaces. In each kidney a relatively deep stellate scar, 7 by 3 mm., extended into the cortex for a short distance. In one or two areas in each kidney there were indistinct, broad, flat-based scars which involved only the superficial portions of the cortex. The dark red blood pyramids of both kidneys contrasted sharply with the pale red-brown cortical regions.

Examination of the abdominal contents was not remarkable. There was no evidence of vascular occlusion.

It can be seen that the principal disease which gave rise to the signs and symptoms presented by this patient was one which produced dilatation of the heart and, subsequently, hypertrophy to an advanced degree.

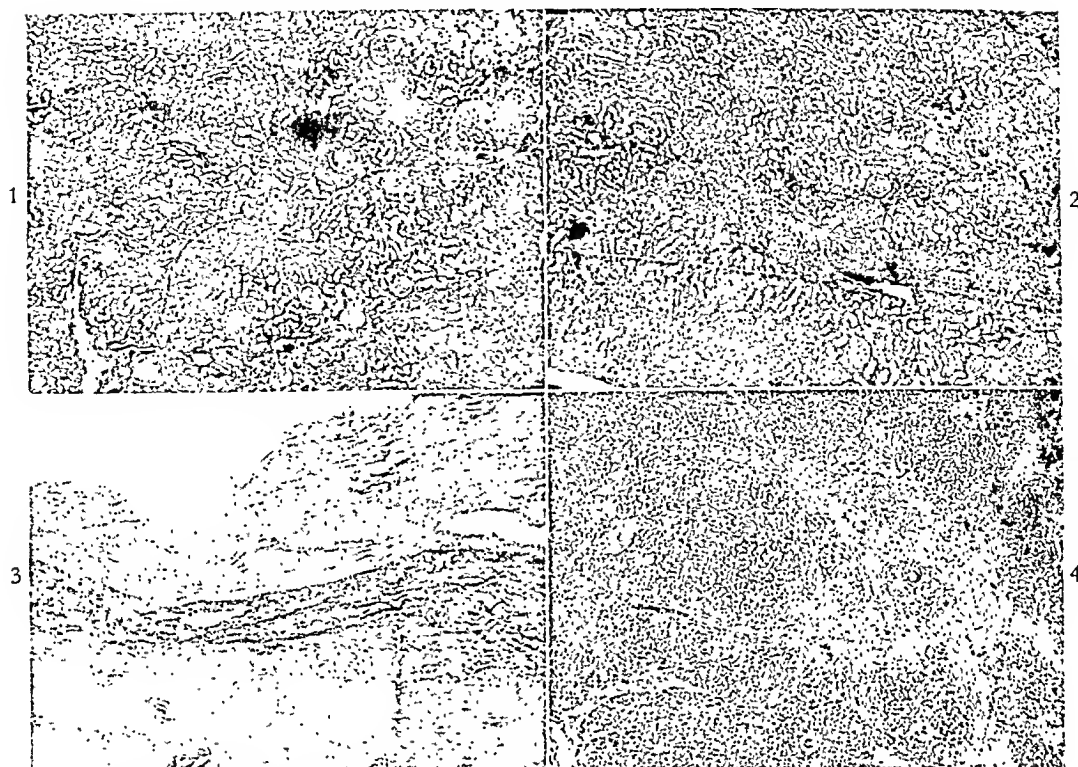


FIG. 1. Section of one kidney showing a slight degree of chronic pyelonephritis.

FIG. 2. A section of the other kidney with changes similar to those in Figure 1.

FIG. 3. Low power view of the wall of the aorta showing changes in the intima due to arteriosclerosis and changes in the media and adventitia which are those of syphilitic aortitis.

FIG. 4. Section of the liver showing an area of fibrosis. The general picture is that of long-standing chronic passive congestion leading to congestive cirrhosis.

Categorically, there are four common types of heart disease which result in dilatation and hypertrophy: these include rheumatic heart disease, syphilitic heart disease, hypertensive cardiovascular disease and congenital anomalies. In this case congenital anomaly may be eliminated on the basis of gross examination. If the enlarged heart were the result of rheumatic or syphilitic disease, one would ordinarily expect to find profound damage in the cardiac valves rather than the relatively minor changes noted in this instance. Likewise, the extent of the anatomic lesions noted grossly in the kidneys and vascular system hardly seems adequate to explain the amount of hypertrophy observed in the heart. Therefore, in order to reach satisfactory conclusions regarding the nature of the disease, we must turn to the microscopic sections and attempt to integrate them with the clinical findings and gross observations.

Figures 1 and 2 illustrate changes which are representative of those seen in both kidneys. There is slight to moderate thickening of the walls and narrowing of the lumina of small and medium-sized arteries in the renal substance. In an area not illustrated here a deep scar extended from the cortex to the corticomedullary junction; the glomeruli within the involved region were obliterated and there was loss of tubular structure. These changes are characteristic of arterial scars but have little if any clinical significance. In the sections shown there are a few irregular and poorly defined foci of lymphocytes and larger mononuclear cells within the interstitial tissue. However, this change, which represents a slight degree of pyelonephritis, is so limited that it may be readily concluded that the pathologic changes within the kidney are not adequate to account for the tremendous hypertrophy of the heart.

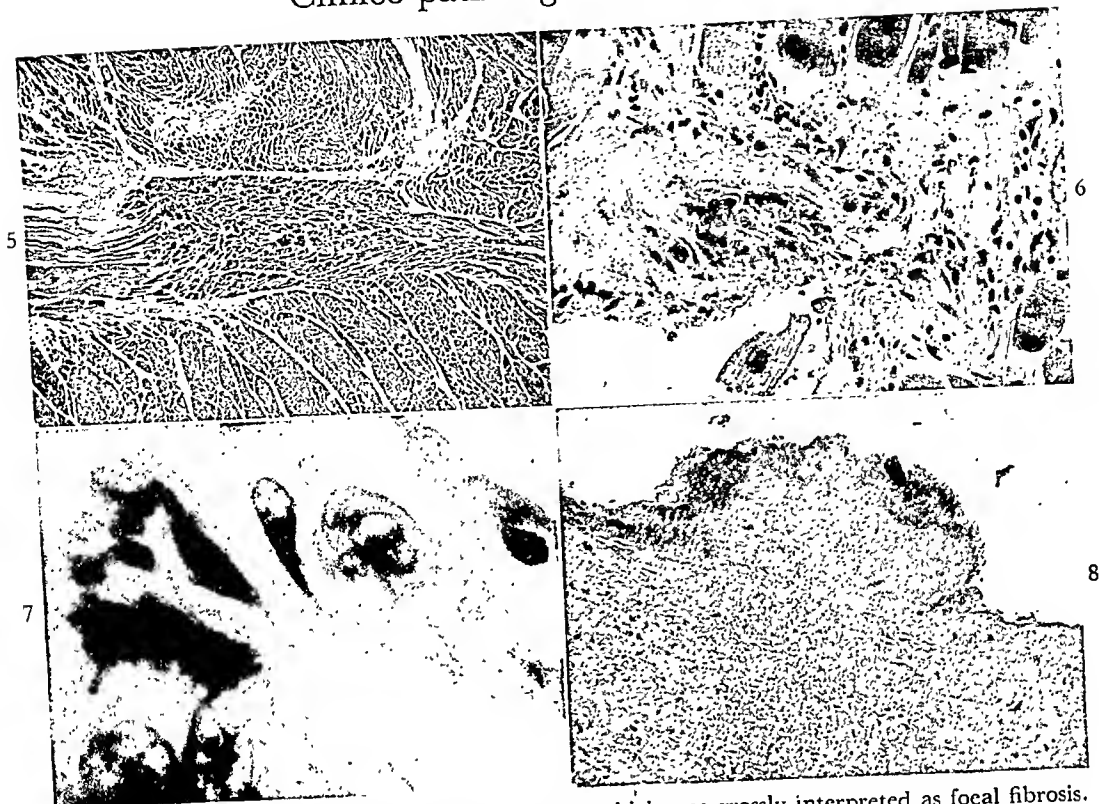


FIG. 5. A section of the myocardium from an area which was grossly interpreted as focal fibrosis. Note the loss of individual myocardial fibers and the replacement of groups of fibers by fibrous tissue.

FIG. 6. Another area of the myocardium showing the characteristic changes of fibrinoid degeneration and infiltration of inflammatory cells characteristic of an Aschoff body.

FIG. 7. High power view of the section in Figure 6 showing an Aschoff cell.

FIG. 8. Section of a verrucous vegetation on the endocardial surface of the left atrium.

A section of the aorta (Fig. 3) was taken to include the intima, media and adventitia from a region grossly thought to show syphilitic aortitis. The anatomic changes in the intima are the result of arteriosclerosis but another lesion is also present. In the media there are irregular, indistinct foci where the elastic tissue has been destroyed and has been subsequently replaced by fibrous tissue in which numerous small vessels are present. Some of the vessels are partially surrounded by lymphocytes and by an occasional plasma cell. Further, the adventitia is thickened by fibrous tissue and the vessels in the adventitia are thickened and irregularly surrounded by inflammatory cells such as those seen in the media. This lesion is characteristic of that seen in syphilitic aortitis. However, in the absence of an accompanying significant complication such as syphilitic valvulitis or stenosis of the coronary vessels, neither of which

was present here, it is not possible to explain the cardiac hypertrophy on the basis of syphilitic infection.

A study of the microscopic changes in the liver (Fig. 4) gives evidence that the process which resulted in cardiac hypertrophy and subsequent decompensation was present sufficiently long that congestive cirrhosis of the liver developed. There is a diffuse increase in dense fibrous tissue throughout the portal regions and in some areas strands of fibrous tissue interlaced about individual isolated hepatic cells which are large and binucleated. In other areas broad bands of fibrous tissue surround hepatic cells grouped in lobule-like masses which contain no central vein. Some central veins are discernible, but most of these are surrounded by irregular foci of fibrous tissue which tend to extend along the sinusoids and join with the fibrous tissue in portal regions. There is infiltration with small and

large mononuclear cells which occasionally appear in small irregular groups of fifteen to twenty-five cells. The central veins and sinusoids in many instances are engorged with blood.

Turning to the heart, Figure 5 represents a section of the myocardium taken from an area interpreted grossly as exhibiting focal fibrosis. There is appreciable loss of myocardial fibers individually and in groups with subsequent replacement by moderately dense fibrous tissue. Occasionally the fibrous tissue is loose and edematous and a few lymphocytes and myocytes are scattered through the interstitium. In Figure 6 it is seen that in regions adjacent to certain blood vessels the collagenous fibrils are swollen and the collagen stains deeply acidophilic. Such a change is designated as fibrinoid degeneration and represents the initial stage in formation of an Aschoff body. Associated with such areas of degeneration in the interstitial tissue are irregular focal accumulations of round cells which are larger than lymphocytes but resemble them insofar as the nucleus is deeply basophilic and dense and the cytoplasm scant. Within such areas of inflammatory infiltration, minute foci of necrosis are observed in some instances. Frequently the large cells, which we know as Aschoff cells, are present (Fig. 7) within the nodular foci. These cells are characterized by an abundant amount of basophilic cytoplasm, the outline of which is irregular. The prominent nucleus is vesicular and contains a heavy bar-like nucleolus. In Figure 7 the nucleolus is indistinct but when one examines the section under the microscope and alters the focus, the character of the prominent hyperchromatic nucleolus can easily be made out.

Sections taken from the mitral valve showed the inner portions to be composed chiefly of altered collagen which was fragmented and deeply acidophilic. Especially at the base of the valve there were numerous lymphocytes, mononuclear cells, polymorphonuclear leukocytes and large irregular cells with abundant amphophilic cytoplasm

and deeply basophilic nuclei. Throughout the valve there were several small blood vessels, a few of which were obstructed by partially organized thrombi. The endocardium covering the valve was slightly elevated by loose edematous fibrous tissue infiltrated with lymphocytes, larger mononuclear cells and a few polymorphonuclear leukocytes, some of which were eosinophiles. In Figure 8 one such section taken from the endocardial surface of the left atrium is shown. In a nodular focus, measuring 2 by 2 by 1 mm., the endocardium has been lifted by a mass of altered connective tissue elements which have undergone fibrinoid degeneration. At one point the endocardium is eroded and a thin layer of fibrin containing cellular debris is deposited over the surface. This lesion is characteristic of the verrucous endocarditis which is frequently observed during the course of acute rheumatic fever.

Within the limitations of our present knowledge, one may conclude that the Aschoff body, characterized by the distinctive features which have been enumerated, is found only in acute rheumatic fever. Investigation by various workers, among them Gross, indicate that the duration of Aschoff bodies in a rheumatic process is from four to six months and that after this period there is healing. In various sections taken from the heart of this patient different stages in the healing process could be found. Thus, in some areas there were fully developed characteristic Aschoff bodies whereas elsewhere less well defined nodular foci were noted in which the large irregular cells were becoming elongated and resembled fibroblasts. Finally, there were irregular foci where inflammatory cells were either minimal in number or were not present at all, and there was replacement of the myocardium by fully developed dense fibrous connective tissue. The latter changes represent the final changes in the recession and healing of the Aschoff bodies.

With respect to this patient, therefore, one may conclude that some years ago she had an attack of acute rheumatic fever

which subsequently receded and produced focal fibrosis of the myocardium. Following the initial stage at intervals which cannot be determined accurately, she had additional attacks of acute rheumatic fever, each of which added insult to the previously damaged myocardium resulting in hypertrophy of an advanced degree. Finally, within the last four to six months, as indicated by the presence of characteristic Aschoff bodies and well formed verrucae on the endocardial surface of the left atrium, the patient suffered still another attack of acute rheumatic fever which added more stress and strain to an already overworked heart. The terminal phase then was one of acute cardiac decompensation in a patient whose heart was markedly enlarged

and unable to compensate for the damage incurred.

Anatomic Diagnosis: Acute rheumatic pancarditis; Aschoff bodies in the myocardium; verrucous endocarditis of the endocardium of the left atrium; focal fibrosis of the myocardium; fibrous thickening of the mitral and tricuspid valves and slight thickening of the chordae tendineae; fibrous adhesions between the cusps of the aortic valve and of the pulmonary valve; hypertrophy and dilatation of the heart (810 Gm.); moderate chronic passive congestion of the lungs, liver, kidneys, spleen and intestines; congestive cirrhosis of the liver; moderate acute bronchitis; syphilitic aortitis; slight chronic pyelonephritis.

Thiouracil Hepatitis*

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TOXIC manifestations of thiouracil have been reported with increasing frequency as the use of this drug for the treatment of thyrotoxicosis has become more general. Agranulocytosis, leukopenia, drug fever, lymph node and glandular enlargement, skin reactions, edema of the feet, psychotic manifestations, albuminuria and hematuria have all been reported as directly due to thiouracil.¹⁻⁶ Gargill and Lesses² were the first to consider thiouracil a hepatotoxic agent. They reported two cases of jaundice in forty-three patients treated. The picture so simulated obstructive jaundice that a laparotomy was performed in one case but no obstruction was found. A biopsy of the liver was taken and it revealed the bile capillaries to be distended and empty in the outer half of the lobule and filled in the inner half. The central veins were prominent. The entire picture appeared to be one of acute biliary stasis and resembled the syndrome of post-arsphenamine jaundice due to intrahepatic biliary tract obstruction.⁶ Moore¹ reviewed 1,091 cases in which the patients were treated with thiouracil and mentions ten cases of lymph node or glandular enlargement in a total of 458 reporting the presence or absence of this complication. He mentions the occurrence of jaundice as a complication. In the discussion of this report Paschkis mentions two cases of agranulocytosis with evidence of jaundice and abnormal bromosulphthalein retention. Recently Livingston and Livingston⁷ reported agranulocytosis and hepatocellular jaundice secondary to propylthiouracil therapy.

The following case is presented as an instance of hepatitis secondary to thiouracil medication:

CASE REPORT

A twenty-seven year old colored female entered the hospital August 17, 1946, complaining of a mass in the neck and choking spells. She stated that she had noticed a gradually increasing fullness in the neck since the birth of her child two years previously. In spite of a ravenous appetite her weight had dropped from 123 to 93 pounds during this period. For the past year she had noticed increasing nervousness and fatigability. Her eyes began to bulge a few months prior to hospitalization. She also noticed some shortness of breath and edema of the feet. For three or four weeks prior to hospitalization there was a dry, non-productive cough but no hemoptysis. She had some dizziness and ringing of the ears. She had frequent attacks of diarrhea with ten loose stools a day. There was no history of melena or icterus.

The patient had irregular menses for the past year and amenorrhea since June, 1946. Her family history and past history were non-contributory.

Physical examination revealed an asthenic colored female with evidence of recent weight loss. The skin was warm and moist. There was moderate bilateral exophthalmus. The eye, ear, nose and throat examination was otherwise negative. There was a large non-nodular, diffuse, firm, bilateral enlargement of the thyroid gland. The chest was normal. There was no enlargement of the heart. There was a soft systolic murmur at the apex. The pulse rate was 110 and the blood pressure was 150/50. Examination of the abdomen was negative. There was slight pitting edema of both feet. Pelvic examination was essentially negative. The reflexes were equal and slightly hyperactive bilaterally.

The serum N.P.N. on August 19, 1946, was 41 mg. per cent and the total proteins were 7.6 Gm. per cent. The Kline and Kahn tests were negative. Urinalysis revealed a specific gravity of 1.014, a faint trace of albumin, was

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negative for sugar and had occasional hyaline casts, leukocytes and erythrocytes. The hemogram revealed a hemoglobin of 10 Gm., 64 per cent; red blood cells 3,600,000; white blood cells 5,650, with 56 neutrophils, 37 lymphocytes, 5 monocytes and 2 eosinophiles. The serum cholesterol was 71.8 mg. per cent and the cholesterol esters were 26.7 mg. per cent. The basal metabolism rate was plus 71. The arm to tongue circulation time was 12 seconds. An electrocardiogram revealed a rate of 100, P-R interval of .16 second; a QRS interval .06 second. The P waves were prominent with sharp peaking of P_2 and P_3 . The QRS axis was plus 80 degrees. The T_4 was deeply inverted. A roentgenogram of the chest revealed the heart to be slightly enlarged without characteristic configuration. The lung fields were clear. Views of the skull revealed the sella turcica to be within normal limits.

A diagnosis of thyrotoxicosis was made and it was decided to prepare the patient for surgery with thiouracil since propylthiouracil was not available at this time.

The patient was placed on a 4,500 calorie high protein diet, complete bed rest, phenobarbital 1 gr. three times a day, with a high intake of vitamins.

On August 20th the patient developed a severe follicular tonsillitis, with temperature elevation and cervical adenopathy. The swelling in the retrocervical region was so intense that a peritonsillar abscess was suspected but none was found. The leukocyte count was 5,300 with a normal differential. On August 21st she was placed on penicillin 30,000 units every three hours and this was continued for seventy-two hours. During this time the temperature dropped to normal and the tonsillar redness and swelling cleared. However, the cervical adenopathy persisted.

During a one-week observation period the pulse rate continued at about 100. She would also run an occasional temperature up to 101°F. She had gained 2 pounds in weight. On August 29th the patient was placed on thiouracil, .2 Gm. twice a day. Because of the exophthalmus she was also placed on thyroid, 1 gr. daily. The leukocyte count was checked three times weekly and varied from 3,000 to 7,850 with the majority of counts varying from 4,000 to 5,000. There was no change in the differential. No depression of the granulocytic series was found. The weight remained stationary and the tem-

perature continued to spike between 98° and 101°F. daily but occasionally was up to 103°F.

The agglutination series revealed typhoid 'O' and 'H' positive 1:40, para B positive 1:40, B. abortus negative and Proteus OX19 positive 1:40. Stool cultures were negative for E. typhi. There had been moderate improvement clinically. The basal metabolism rate on September 19th was plus 14.

On September 16th (eighteen days after the start of thiouracil therapy) the patient developed slight jaundice. The icterus index was found to be 33.6 units. Because of the possibility that thiouracil might be causing the jaundice, the drug was immediately discontinued. A blood fragility test in the patient revealed hemolysis beginning at .42 per cent and not complete at .24 per cent, while a control started at .44 per cent was complete at .32 per cent. The serum cholesterol on September 23rd was 148 mg. per cent. The urine was negative for urobilinogen. A diagnosis of hepatitis was made and the patient was placed on a high carbohydrate, high protein, low fat diet with infusions of glucose, with methionine 1 Gm. three times a day. The thyroid extract was discontinued on September 18, 1946.

The temperature now varied from 98.6° to 99.4°F. daily with only rare spikes to 100°F. The pulse varied from 70 to 100. Supportive treatment for hepatitis was continued but the icterus index gradually rose. The van den Bergh test was immediate and direct on October 4, 1946. The serum cholesterol was 161.9 and cholesterol esters were 71.3 on October 11th. The prothrombin time was 82 per cent of normal and the icterus index was 96.5 units on October 17th. The cephalin-cholesterol flocculation was 2 plus; total proteins 7.7 Gm. per cent with albumin 3.4 Gm. per cent and globulin 4.3 Gm. per cent. The N.P.N. was 27 mg. per cent. The urine was repeatedly negative for urobilinogen. The stool was negative for urobilinogen on October 19th. The oral hippuric acid liver function test revealed .80 Gm. excreted in one hour. The jaundice became so intense that a common duct stone was considered. A cholecystogram on October 23rd revealed non-visualization of the gallbladder.

The lymph nodes became generally palpable on October 5th and the possibility of a generalized reticuloendotheliosis was considered. Biopsy of a cervical node was done

and was reported to show simple hyperplastic lymphadenitis.

On October 26, 1946, the patient developed paranoid tendencies. The liver became palpable; the spleen became questionably palpable. The leukocyte count dropped to 2,000 after thiouracil was discontinued and remained between 3,000 to 5,000/eu.mm. The differential was normal. The hemoglobin dropped to 8.3 Gm. and the patient was given blood and plasma. On August 30th the ieterus index was 130. The patient expired on November 13, 1946.

The temperature had maintained a low rise from 98° to 99.6°F. daily during the last few weeks of her illness and rose to 104°F. prior to her death. The pulse varied from 80 to 100 but rose to 160 prior to death. Her respirations were 20 but rose to 34.

Postmortem Examination. The autopsy revealed an emaciated colored female who appeared to be about the stated age. The sclerotics were rather deeply jaundiced and there was sordes of the lips and tongue. The thyroid was diffusely enlarged both to palpation and inspection. The cervical lymph nodes were palpable. The breasts were atrophic and the abdomen was scaphoid. There was a superficial bed sore in the sacral region. The external genitalia appeared normal and the thighs and legs were symmetrically equal and free from pitting edema. The subcutaneous adipose tissue was very scant.

The pleural cavities were free from adhesions and fluid. The right lung weighed 500 Gm. and the left 360 Gm. The right upper lobe was firmer than normal and the pleura over the dependent aspect of the upper and lower lobes was dark red and glistening. Section revealed areas of dark red consolidation measuring from 1 to 2 cm. in the dependent portions of both the upper and lower lobes, and moderately diffuse edema. The left lung showed dependent congestion and edema. The bronchi contained a little mucus and froth and showed yellowish-red lining. The peribronchial lymph nodes were moderately enlarged and black and a calcified node was present on each side. The pericardial layers showed a yellowish tint and the sac contained approximately an ounce of clear yellowish fluid. The heart weighed 290 Gm. and was conical in shape. The right ventricle was moderately dilated and its wall measured .5 cm. in thickness. The myocardium was dark red, wet, of normal consistency and free from gross

sears. The valve leaflets showed an icteric tint. The coronary ostia and arteries showed no evidence of disease. The lining of the aorta was smooth and light yellow. The thyroid was symmetrically enlarged and weighed 90 Gm. The fissures of lobulation on its external surface were accentuated and the capsular blood vessels were prominent. The cut surfaces were brownish-red and opaque. No nodules were present.

The base of the tongue showed considerable nodular irregularity due to hyperplasia of lymphoid tissue. The left tonsil was enlarged and somewhat pedunculated. The superficial and deep cervical lymph nodes on the right were enlarged, soft and pink. The thymus weighed 20 Gm. and was salmon-pink in color. The larynx and trachea appeared normal other than slightly icteric. The lining of the esophagus was smooth and showed a yellowish tint. The stomach was of average size and its lining was mottled gray and pink. The small and large intestines showed nothing noteworthy.

The mesenteric lymph nodes measured as much as 1 cm. in diameter and in some instances showed purplish color. The pancreatic and hepatic nodes were moderately enlarged and of a brownish red color. The retroperitoneal lymph nodes were not enlarged. The peritoneum was of a grayish pink color, dry and free from adhesions. The spleen was free from adhesions and weighed 120 Gm. Surfaces made by section were grayish red, moderately soft and the malpighian bodies were distinct but not large. The liver weighed 1,080 Gm. and slight shallow fissuring was noted on the anterior surface of the right lobe just above the lower edge. However, definite nodulation was not present. The capsular surface tended toward an olive-green color. Surfaces made by section were brownish red with a greenish tint, and the lobular etching was fairly distinct. The extrahepatic bile ducts and gallbladder showed nothing noteworthy. The pancreas weighed 90 Gm. and was grayish pink in color. Section revealed distinct lobular architecture. The adrenals had a combined weight of 18 Gm., the left being a little larger than the right. The cortices were of regular and average thickness and were yellowish red in color. The medullae were soft and brownish red. The kidneys were of about equal size and had a combined weight of 290 Gm. Their capsules stripped easily exposing smooth brownish red surfaces. The cut surfaces showed a similar color, were moist and glistening and the archi-

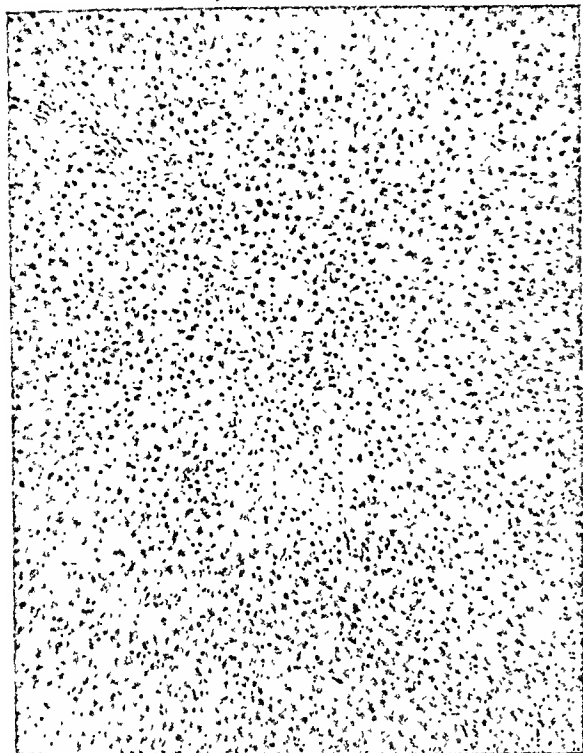


FIG. 1. Section of liver showing area of focal necrosis.

tectural features were fairly distinct. The renal pelvises, ureters and urinary bladder showed nothing noteworthy. Other than erosion of the cervix, the uterus and adnexa showed no noteworthy change.

The marrow in the sternum and lumbar vertebrae was brownish red in color and in the sternum it was soft. The brain and meninges were negative for gross lesions.

The microscopic examination of the thyroid showed marked epithelial hyperplasia, reduction of the colloid but no lymphoid hyperplasia. The epithelium was tall and columnar and showed numerous papillary infoldings into the acini. The colloid stained poorly, contained desquamated epithelial cells and showed marginal vacuolization. Moderate diffuse fibrosis of the myocardium was noted in the sections from the heart. Sections from the consolidated areas of the right lung revealed a purulent exudate in the bronchi and surrounding alveoli. In sections not showing an inflammatory reaction the alveoli were filled with a pink-staining, homogeneous fluid. In addition to old fibrocaseous tuberculosis of the peribronchial lymph nodes an occasional fresh tubercle with a necrotic center was noted. The sections from the enlarged cervical and abdominal lymph nodes revealed distention of the sinuses with endo-

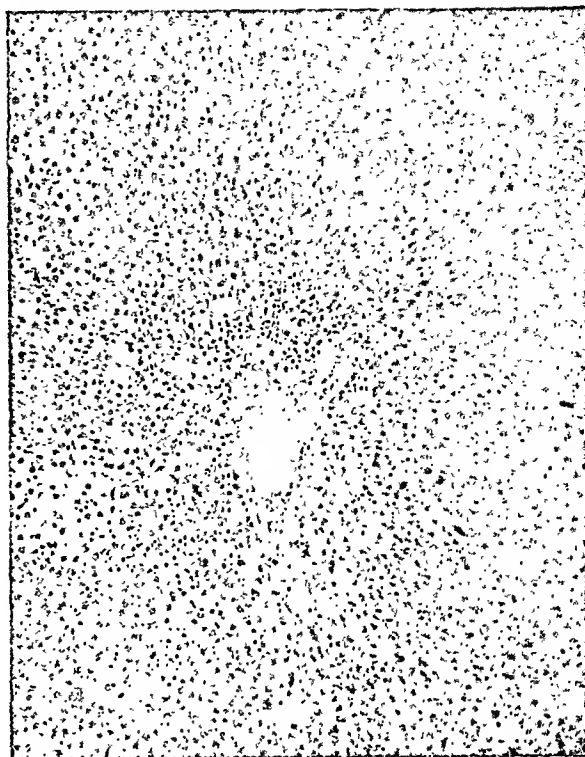


FIG. 2. Section of liver showing central necrosis, with hyaline thickening of the central vein wall with necrosis, disorganization and some cellular infiltration of the hepatic cells.

thelial cells associated with a sprinkling of leukocytes (sinus catarrh).

The spleen was congested and showed moderate reticulosis and infiltration by polymorphonuclear leukocytes and plasma cells. The germinal centers of some of the follicles were necrotic. Fibrosis (mainly interlobular) and focal postmortem necrosis was noted in the pancreas. The thymus was hyperplastic for this age. The sections from the kidneys revealed fairly extensive calcification of the lower portion of the collecting tubules. There were also bile casts and degenerative changes of the tubular epithelium.

The liver showed both focal and central necrosis. (Figs. 1 and 2.) The center of almost every lobule presented a rarefied disorganized appearance, indicating disappearance of hepatic cells. Many of the remaining central cells exhibited karyolysis and pyknosis. Slight polymorphonuclear leukocytic infiltration was frequently observed in the central areas. Endophlebitis of the central and sublobular veins was fairly widespread. This was frequently represented by hyaline thickening of the walls of the veins but not infrequently an earlier stage was

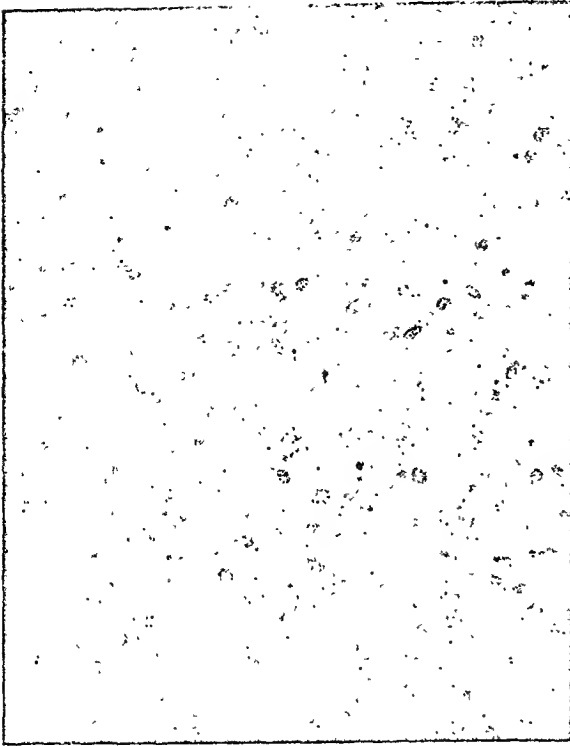


FIG. 3. High power from central zone showing so-called "bile casts" and necrobiosis.

encountered, characterized by swelling and proliferation of the endothelial cells and slight cellular inflammatory reaction. Central bile pigmentation (hepatic cells laden with a greenish yellow pigment) and plugging of the bile canaliculi centrally by so-called bile casts were much in evidence. (Fig. 3.) Rarely one encountered small foci of necrosis in the mid-zone of the lobule which might or might not be contiguous with an area of central necrosis. In the subcapsular region an irregular pattern of scarring interpreted as residual to more remote hepatic injury was encountered.

In places, chiefly in the zona reticularis, the adrenals showed a disorganized appearance with loss of the parenchymal cells and consequent prominence of the scaffolding element. The sections from the brain, bone marrow, uterus and adnexa showed no noteworthy change.

The anatomic and microscopic diagnoses were exophthalmic goiter, bronchopneumonia, slight hypertrophy and fibrosis of the heart, calcified, fibrocaseous and miliary tuberculosis of the peribronchial lymph nodes, simple lymphadenitis (sinus catarrh) of the cervical and abdominal nodes, moderate acute hyperplasia of the spleen, hyperplasia of the thymus, fibrosis

and focal postmortem necrosis of the pancreas, necrobiotic change in adrenals, focal and central necrosis of the liver associated with area of fibrosis in the subcapsular region, bile nephrosis and metastatic calcification of kidneys and jaundice.

COMMENT

The hepatic damage in this case could be due to both the thyrotoxicosis and the thiouracil. However, it is doubtful that it was due to the former because the jaundice occurred when the toxemia associated with thyrotoxicosis was decreasing, as shown by the falling basal metabolism rate and general clinical improvement. Since no other hepatotoxic substance was administered, it is concluded that the thiouracil was the etiologic factor. Although this is a rare complication of thiouracil therapy, it must be considered an important one. The patients in the cases previously reported have recovered. However, this patient was in such a severely debilitated state that she was unable to survive in spite of general supportive measures.

SUMMARY

A case of hepatitis which occurred subsequent to thiouracil is presented, with autopsy findings.

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Rupture of Splenic Infarct and Sudden Death Complicating the Course of Subacute Bacterial Endocarditis*

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RUPTURE of a splenic infarct from any cause is rare. Blumer¹ in 1923 reported a series of 150 autopsies in patients dying of subacute bacterial endocarditis in which there were 115 splenic infarcts. Of these infarcts, sixteen were septic in character. No mention was made of rupture of any of these splenic infarcts. Todd² in 1919 described a case of ruptured splenic infarct, with resultant hemorrhage and death. The etiology in this case was a gunshot wound of the leg, with an infected compound fracture complicated by septic embolism of the spleen. Billings³ in 1929 reported a case of splenic abscess of unknown origin which caused generalized peritonitis and death by rupture into the peritoneal cavity. Wolfson⁴ in 1944 stated that when abscess of the spleen occurs as a complication of subacute bacterial endocarditis, operation is contraindicated because of the grave prognosis of the underlying disease.

The first case of rupture of the spleen in the course of subacute bacterial endocarditis was cited by Lake et al.⁵ in 1919. In this case ulceration through the splenic artery had occurred. Vallee,⁶ also in 1919, described a case. In 1926 Krokiewicz⁷ attributed rupture of the splenic infarct in his case to paroxysmal increases of blood pressure when the patient strained at stool. Pallasse et al.⁸ in 1931 attributed death in their case to rupture of a hemorrhagic splenic infarct. Braxton-Hicks⁹ in 1932 described a fifteen year old girl who at

autopsy showed no evidence of splenic infarction. However, there was marked necrosis of the lower half of the spleen, with rupture through the capsule. The case of Kerkhof et al.¹⁰ in 1933 was that of a seventeen year old boy. Death here was also due to ruptured splenic infarct and subsequent hemorrhage. Willius¹¹ in 1935 described a twenty-three year old male whose exitus was prompted by rupture of a mycotic aneurysm of the splenic artery. Fingerland¹² in 1938, Rantz et al.¹³ in 1943, Mallory¹⁴ in 1946 and Hertzog et al.¹⁵ also in 1946 reported similar cases of subacute bacterial endocarditis, with rupture of the spleen and subsequent death.

There are many reports of spontaneous rupture of the spleen due to causes unknown as well as to definite etiologic factors. There are also many case reports of splenic infarction, with or without abscess formation, in which the spleen did not rupture. However, a careful perusal of the medical literature to date reveals only eleven case reports of subacute bacterial endocarditis complicated by rupture of the spleen. The following case is cited as an addition to this group:

CASE REPORT

E. J. was first admitted April 28, 1946. In February, 1946 this twenty-seven year old white male had some teeth extracted while he was suffering from the "grippe," and was running a slight temperature. Two weeks later he noted onset of chills, fever, sweats and loss of appetite.

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These symptoms became progressively worse, finally reaching the point at which he was incapacitated. He then consulted his physician who examined him and promptly took a blood culture. The blood culture was positive for streptococcus viridans on April 28th and the patient entered the hospital for treatment of subacute bacterial endocarditis.

Past history revealed that the patient had been a normal baby at birth. He had the usual childhood diseases plus tonsillitis in infancy. His tonsils were removed at an early age. There was no history of scarlet fever, rheumatic fever, growing pains or frequent sore throats. He had never experienced a serious illness and was active in athletics in high school. His occupation was that of a machinist.

Family history was completely negative. No familial tendencies were elicited.

Review by systems was essentially negative, except for the present illness.

Physical examination on admission showed the patient to be a well developed, well nourished white male, not cyanotic or dyspneic, but appearing feverish and somewhat dehydrated. The skin was clear. No petechiae were noted. The head was essentially negative. The pupils were round, regular and equal and reacted to light and accommodation. There was no scleral icterus. The ears were negative to external examination. The nasopharynx was clear. A few teeth were missing and the remaining ones were very carious. The thyroid was not enlarged, and there was no palpable adenopathy or venous distention. The chest was clear to percussion and auscultation. The heart was enlarged to the left and down. No thrills were noted. There was a harsh, blowing systolic murmur heard best at the third and fourth interspaces to the left of the sternum and transmitted to the base and left axilla. Occasional extrasystoles were heard. The blood pressure was 180/80. Examination of the abdomen revealed no palpable organs or masses, no tenderness, spasm or hernias. Examination of the genitalia was negative, and the rectal examination was not significant. There was no cyanosis, clubbing or edema of the extremities. The peripheral pulse was regular, except for occasional dropped beats.

Laboratory results on admission were as follows: Red blood cells, 4,100,000, with a hemoglobin concentration of 78 per cent; white blood cells, 7,800, with 80 per cent neutro-

phils, 18 per cent lymphocytes and 2 per cent monocytes. Non-protein nitrogen was 33.7 mg. per 100 cc., and the fasting blood sugar was 111 mg. per 100 cc. The urine was acid, with a specific gravity of 1.023, and was negative for albumin, sugar, red blood cells and casts. The blood culture was positive on April 28th for streptococcus viridans.

Diagnosis of subacute bacterial endocarditis was made, and congenital heart disease, potentially cyanotic in type, probably an interventricular septal defect, was considered.

The patient was put on a regimen of 50,000 units of penicillin, intramuscularly every four hours, and $\frac{1}{2}$ Gm. of sulfadiazine orally every four hours, with sufficient sodium bicarbonate to keep the urine alkaline. This was continued until June 8th, after which the penicillin was administered in 1,000 cc. of 5 per cent glucose in water, 1,000,000 units daily. This was kept up until July 1st even though the blood culture was reported negative on June 18th. A total of 36,300,000 units of penicillin was administered during this admission.

During his hospital stay the patient developed what was thought to be a patchy type of bronchopneumonia in the face of all the medication he received. This process gradually subsided. His temperature curve was septic in type for the first five days, and then gradually dropped to between 99°F. and 100°F., at which level it hovered for the next six weeks, with daily spikes. The temperature slowly returned to normal toward the end of his hospital stay. He was discharged on July 1st markedly improved.

After one week at home the patient noted return of his previous symptoms and even though the blood culture was still negative, entered the hospital on July 21, 1946 for further intensive treatment. This time he received 1,000,000 units of penicillin daily, in 1,000 cc. of normal saline by intravenous drip, from July 21st to August 19th. That made a total of 30,000,000 units of penicillin for this admission.

Although his admission temperature was only 100°F., he ran a spiking course similar to his previous admission, gradually returning to a normal temperature a few days before discharge. The symptoms gradually subsided and no new symptomatology was noted. A chest x-ray on August 6th showed evidence of an old left hilar infarction in the same area that the pneumonia was thought to have occurred.

The interval between the second and third

admissions was three weeks during which the patient again noted onset of the previous chills, fever, anorexia and sweating. The blood culture was again positive on September 10th and he entered the hospital for the third time for further intensive treatment.

The physical examination was essentially unchanged from those on former admissions, except for the heart. There were still no petechiae, no enlarged nodes or organs. The cardiac findings had changed somewhat. At this time the patient had a harsh systolic murmur over the whole precordium, heard best in the fifth interspace to the left of the sternum. The second sound was replaced by a diastolic murmur, heard over the whole precordium but best heard over the aortic area. The blood pressure was 150/80 in both arms and 225/85 in the legs. The laboratory results were not significantly changed. At no time was there any hematuria, gross or microscopic.

Penicillin was once again begun, at the rate of 2,000,000 units a day, in 1,000 cc. of normal saline intravenously. It was stopped on September 29th because the blood culture had turned negative. The blood culture again became positive on October 10th, and penicillin was once more started in the same dosage until October 31st. Penicillin was then discontinued until November 11th when a dosage of 3,500,000 units a day was administered in 2,000 cc. of normal saline intravenously for the next five days. It was then stepped up to 5,000,000 units daily for the following five days.

Several penicillin blood levels were taken during the last admission, and the concentration ranged from 0.124 to 4.0 units per cc. Penicillin resistance studies were also made, and the smallest inhibiting amount of penicillin ranged from 0.0625 to 0.5 units per cc. of blood.

During the last week of his illness the patient complained many times of pain in the left upper quadrant of his abdomen which he described as sharp, transient, non-radiating in nature. Physical examination revealed tenderness in this region but the spleen was never definitely palpable. On the evening of November 20th the patient was suddenly seized with severe pain in the left upper quadrant, radiating to the groin, with a sense of fullness in the abdomen. He immediately developed marked respiratory distress, became clammy and pulseless, with an unobtainable blood pressure. In a matter of

minutes he went into irreversible shock despite supportive therapy and expired.

The penicillin dosage during this admission was 122,500,000 units. The total dosage for his entire illness was 188,800,000 units of penicillin.

Autopsy report revealed the following: The body was that of a well developed, well nourished, very pale white male. The pupils were round and equal and there were no conjunctival petechiae. A 5 cm. transverse scar was noted just below the left patella. There were no cutaneous nodules or petechial hemorrhages present on the body. There were a few dense adhesions in both pleural spaces. These were most marked in the apical and midportions of the lung. There was no free fluid. About 10 cc. of straw colored fluid was noted in the pericardial cavity; no adhesions were present. On exposing the peritoneum a dark red appearance was noted. Palpation through the peritoneum revealed the presence of a large amount of fluid. On opening the peritoneum about 4,000 cc. of semiclotting blood was noted. The omental bursa was completely filled with clotted blood. The greater omentum was swung to the left upper quadrant of the abdomen where it had formed a nearly complete envelope about the spleen. The very dense adhesions through this quadrant made the spleen difficult to dissect. The heart weighed 525 Gm. There was both dilatation and hypertrophy; hypertrophy was present in both ventricles, more marked in the left. Dilatation was marked and was confined to the right auricle. The left ventricle measured 30 mm. in thickness and the right measured 18 mm. The right auricle measured 3 mm. in thickness and the left measured 1.5 mm. The orifice of the tricuspid valve was enlarged admitting four fingers with ease. There was thickening and shortening of the chordae tendinae of this valve. Most of the pathologic condition was confined to the mesial leaf of the tricuspid valve. On the atrial surface there were three small, pink, fresh, friable vegetations which could be easily scraped away. These extended up on to the endocardium of the right auricle. There was a foramen on the atrial surface of the mesial leaf of the tricuspid valve measuring 0.4 cm. in diameter. (Fig. 1.) This foramen led down to a pocket, the bottom of which communicated directly with the left ventricular cavity at about the level of the mitral valve, thus forming an interventricular septal defect. The ventricular septum itself in

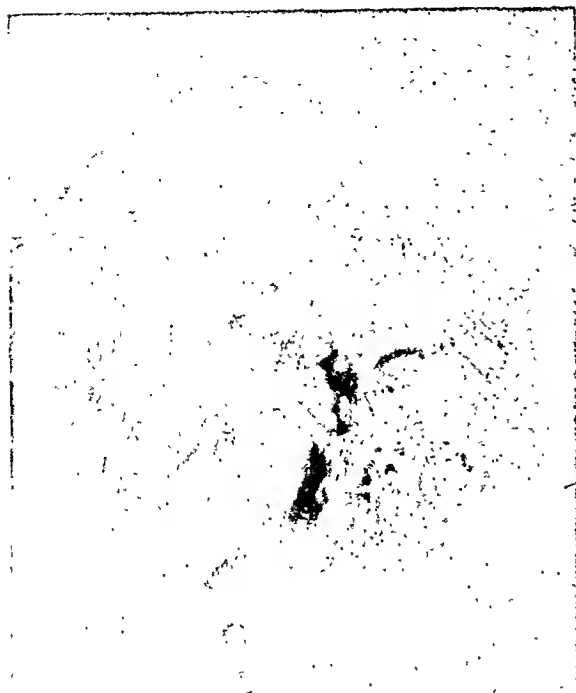


FIG. 1. The right side of the heart, with vegetations present on the tricuspid valve and the opening of the interventricular septal defect into the mesial leaf of the tricuspid valve.



FIG. 2. The spleen, with a large area of rupture and evidence of both old and recent infarction.

this area was thickened and fibrous. The mitral and pulmonary valves were free from disease while the aortic valve revealed small, pink, friable vegetations on the noduli Arantii of all the cusps. There was fusion of one aortic commissure. The myocardium revealed only the hypertrophy previously described. The right lung weighed 320 Gm., and the left weighed 310 Gm. The external surface of both lungs was not unusual, except for a purplish color confined to both lower lobes. Crepitation was absent. Section revealed an obliteration of lung markings in these areas, with replacement by a homogeneous purple color. The liver weighed 1,875 Gm. It was markedly enlarged. It was dark red in color and soft in consistency. Section revealed a nutmeg appearance. The gallbladder and ducts were free from calculi. The spleen weighed 875 Gm. It was swollen, with a tense capsule and its edges were rounded. On exposing the renal surface of the spleen a massive defect was noted, measuring 11 by 7 cm., the depth being best appreciated by the fact that a finger inserted into this defect touched the diaphragmatic surface of the spleen with ease. The diaphragmatic surface was covered with varying sized, rather firm, greyish patches, ranging from 0.5 cm. to 4.5 cm. in diameter.

There appeared to be marked variation in the age of these infarcts. Section of the spleen revealed that these areas were found in some cases to extend as far as 3 cm. into the splenic substance where they formed a cavity filled with purulent material. Most of the splenic parenchyma, especially in the vicinity of the rupture, was soft and mushy and apparently without structure. No abnormalities were found in the gastrointestinal tract, pancreas, kidneys or adrenals.

The myocardial fibers of the heart were mildly hypertrophied. Among them was a single tiny group of polymorphonuclear and mononuclear cells. No Aschoff bodies were seen. Sections of the tricuspid valve showed fibrous thickening and vascularization. There was a low, broad vegetation composed of granulation tissue covered by fibrin and necrotic debris. Beneath the surface were two small calcific deposits. Gram stain revealed a few gram-positive cocci in short chains in two vegetations. There was mild fibrous thickening of some alveolar septa in the lung. There was mild sinusoidal engorgement around the efferent veins of the liver, with increased yellow pigmentation of cells in those regions. In the spleen there were areas of old and recent infarction and some small suppurative infarcts. One large, fresh infarct was hemorrhagic and extended through the capsule. (Fig. 2.) One artery was filled with necrotic debris containing a calcium deposit. A smaller adja-

cent vessel contained a fresh thrombus. No abnormalities were found in the pancreas, adrenals or kidney.

Anatomic Diagnosis: Congenital cardiac anomaly; patent interventricular septum; rheumatic heart disease, inactive; tricuspid and aortic valvulitis; tricuspid insufficiency; cardiac hypertrophy and dilatation; subacute bacterial endocarditis; septic infarcts of the spleen; rupture of the spleen; hemoperitoneum; bilateral atelectasis; chronic passive congestion of the liver.

SUMMARY

1. A review of the medical literature to date revealed only eleven cases of subacute bacterial endocarditis which were complicated in their course by rupture of the spleen and consequent death.

2. A report of another such case is presented in which the mechanism of death was massive internal hemorrhage.

Acknowledgment: The author wishes to express his thanks to Dr. V. M. Maddi from whose private service this case report was taken.

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Complications of Deep X-ray Therapy of Carcinoma of the Lung^{*}

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THE effect of high voltage roentgen irradiation on the human lung has been studied chiefly in connection with the palliative treatment of intrapulmonary extension or metastasis from breast carcinoma. There has usually been abundant clinical material of this nature available, partly due, no doubt, to the fact that there still exists a school of surgical thought believing that radical breast surgery is useless, that just as good results can be obtained after simple mastectomy by turning the patient over to the roentgenologist who is supposed to irradiate and kill any cancer cells remaining in the axilla, pectoral muscles or mediastinum. Such surgeons by this escapist attitude toward the problem are probably harming not only their patients but also the entire cause of adequate cancer therapy. It has been possible, however, from this and other sources to obtain material for the study of x-ray reactions in human tissues, such as is found in the papers of Leach, Farrow, Foote and Wawro,¹ Leach² and Widmann,³ and these will be referred to later in more detail.

In 1940 I reported a study⁴ of a case of a patient with bronchial adenocarcinoma who had received excessive doses of roentgen rays thereby producing a pneumonitis and pleuritis typical of an irradiation reaction. This effect was extensive and severe enough to lead to the death of the patient although the neoplasm remained local, as it was well walled-off by fibrous tissue. The purpose in publishing the case was to draw attention to the dangers of roentgen rays, especially when administered by different operators

each giving courses of treatment without knowing what previous exposures had been incurred. The cumulative effect of such irradiation in this instance caused irreparable damage to lung tissue and resulted in a fatality. Postmortem material of this nature has been and apparently still is uncommon, so another case of primary carcinoma of the lung with complicating roentgen ray reactions in pleura and lung is offered with complete autopsy findings. It is also another illustration of local control of a bronchial (squamous cell) carcinoma by the rays with, at the same time or subsequently, tissue insult far removed from the tumor itself contributing to the fatal outcome.

CASE REPORT

The patient was a white man, forty-nine years of age, who had been under the care of Dr. James V. Barrett of Troy, N. Y., for a chronic cough of eight months' duration. He complained of loss of appetite, strength and weight, and a chestache not definitely localized. There was little sputum, no lymphadenopathy and no known contact with tuberculosis. Dizziness, hoarseness and night sweats had been present for several months. He entered the Pawling Sanatorium on July 18, 1940. At that time his state of nutrition was fair. The only pulmonary signs were inconstant râles in the left lung posteriorly. A roentgenogram then showed a mass at the right hilum, ? tumorous. (Fig. 1.) The descending bronchial trunks were accentuated but there was no parenchymal disease present. A bronchoscopic examination was made on August 7, 1940, and no tumor, either intra- or extrabronchial, was demonstrable. There was no apparent bronchial stenosis but at the tip of the carina there were two areas of redness.

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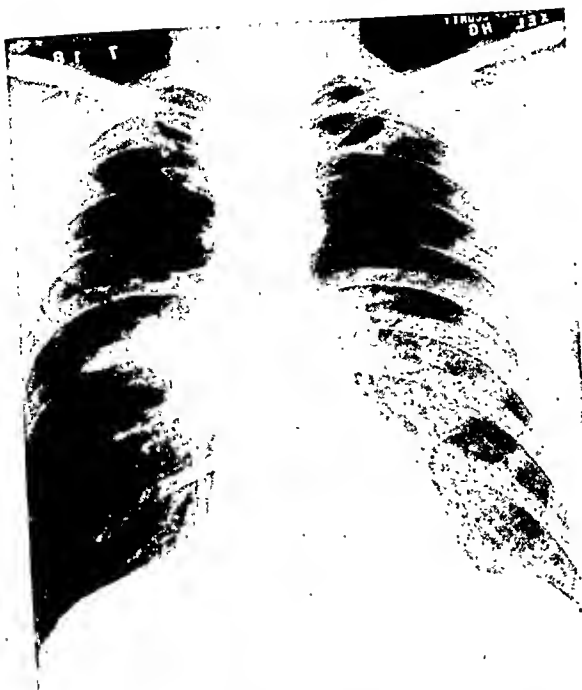


FIG. 1. Chest film July 18, 1940, showing a tumor mass in the region of the right hilum.

On November 6, 1940, he was improved in a general way, and a roentgenogram of the chest showed that the mass noted previously at the right hilum was greatly reduced in size and more indefinite in outline. There was, however, slight mottling in the mid-zone of the right lung. On March 20, 1941, there was no change in the clinical picture, but x-ray showed a wedge-shaped area of density proceeding from the hilum to the base, suggesting atelectasis in the right lower lobe. In May, 1941, he began to have cyanosis and there was dullness with absence of breath sounds throughout the right lung. A roentgenogram showed complete collapse of the right lung and the heart pulled slightly to the right. The finger nails were becoming curved and cyanotic. Cervical lymphadenopathy was detected for the first time. There were frequent cardiac extrasystoles. Blood pressure was 98 systolic and 60 diastolic. Bronchoscopic examinations in April, June and December, 1941 did not reveal any lesion. In December, 1940, a small amount of secretion was seen coming from the right middle bronchus. Sputum examinations were always negative for acid-fast bacilli, but from June to December, 1941, sputum smears and cultures were positive for monilia. Cultures on Petroff's and Dorset's media of material from bronchial aspirations were negative for tubercle bacilli after three months of incubation. There had

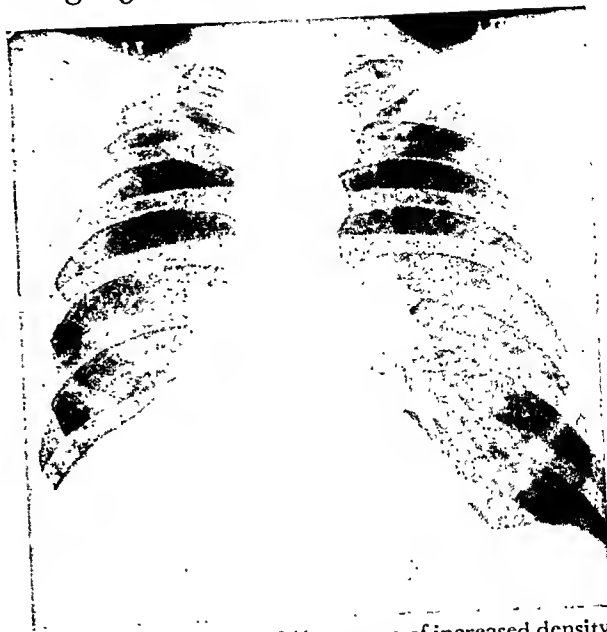


FIG. 2. November 13, 1941, an area of increased density at the right hilum. The descending bronchial trunks are markedly dilated on the right side and arc surrounded by flocculent shadows of inflammatory character. A wedge-shaped area of density extends from the hilum to the base which is typical of atelectasis.

been no rise of temperature. The pulse rate varied between 90 and 112. Atelectasis in May, 1941, with pneumothorax caused marked dyspnea but the lung gradually inflated and breathing became normal. In July, 1941, hematuria developed. The prostate was found greatly enlarged. An intravenous pyelogram was normal. By August, 1941, his general condition was greatly improved. There was less coughing, and no further hematuria. A roentgenogram of the chest no longer revealed any abnormal shadow in the right hilum. There were a few scattered, moist râles in the right posterior mid-zone. Whatever the nature of the condition it was agreed by all observers that it was not clinical tuberculosis.

On October 2, 1941, his temperature was 99°F., pulse 104 and respirations 24. Râles were heard at the extreme right base posteriorly. A chest film showed an area of increased density in the right hilum. The descending bronchial trunks were markedly dilated on the right side and were surrounded by flocculent shadows. The right costophrenic angle was obscured. A diagnosis of bronchiectasis and probable new growth in the right lower lobe was made. Three weeks later he complained of much chest pain, and a roentgenogram revealed again a wedge-shaped area of density which was probably atelectasis in the right lower lobe. (Fig. 2.)



FIG. 3. March 27, 1942, chest film taken in a PA projection with a target-film distance of 7 feet, showing increased density at the right base. This represents a partially atelectatic lobe, but there has been a marked improvement as compared with the previous films. The right hilar shadow is slightly less prominent. The left lung field is relatively clear.

FIG. 4. May 18, 1942, eight days before death. There is a marked increase in density in the upper portion of the right lung and in the region of the left hilum. Most of the extra density is probably due to irradiation pneumonitis rather than due to the tumor.

Blood examination in November and December, 1941 showed hemoglobin 74 to 80 per cent; erythrocytes 3,200,000; leukocytes 15,000; neutrophils 70 per cent, lymphocytes 20 per cent, mononuclears 7 per cent and eosinophiles 2 per cent. Marked poikilocytosis and anisocytosis was present.

On January 12, 1942, at the Memorial Hospital, New York City, a bronchoscopic examination was made by Dr. Watson who found in the right main bronchus 3 cm. below the carina a heaped-up, granulating lesion obstructing the bronchus and having the appearance of a fungating carcinoma. Biopsy was taken and reported "epidermoid carcinoma, grade 3."

About one week after the last bronchoscopic examination the patient developed a severe cough with pain in the right chest. Fluoroscopic examination revealed pneumothorax with about one-half of the lung deflated. A large bulla of about 3 cm. diameter was visible in the upper lobe. The first series of x-ray treatments was given and after six weeks the extra density at the base of the right lung had partially cleared

up. What density remained, Dr. Orville Henderson, roentgenologist, believed was due to irradiation pneumonitis rather than to tumor. Wheezing respiration was greatly relieved by ephedrine. There was gradual loss of weight during this time. A blood leukocyte count on March 20, 1942, was 8,800 and there was a mild hypochromic anemia.

In April, 1942, he was given a second series of deep x-ray exposures. The cough became much less but codeine $\frac{1}{2}$ gr. four to six times daily was still necessary to alleviate pain. The right middle lobe at this time was about three-fourths inflated and the pulmonary shadow much reduced. (Fig. 3.) A summary of the x-ray treatments is as follows:

Deep x-ray therapy was instituted on January 26, 1942 by Dr. Orville Henderson, roentgenologist of the Samaritan Hospital, Troy, N. Y. The current was 22 kv. p., 20 ma., 80 cm. T.S.D., with filter of .5 mm. copper. Fields of the dimension of 15 by 15 cm. were used, one anterior, one posterior and two lateral directed at the right lung. Daily treatments were given with a total of 3,500 r anteriorly, 2,900 r

posteriorly and 2,000 r to each of the lateral fields.

Two weeks later, in April after the first series, severe pain in the right chest was accompanied by a pleural friction rub. There was an increase in the pulse rate to 120 with a temperature of 97.8°F. The right lung showed little expansion with fine râles anteriorly on both sides of the chest and impaired transmission of breath sounds posteriorly in the right lung. (Fig. 4.) On May 19th he was in great respiratory distress, requiring oxygen inhalation. His temperature was 100°F. but there was no increase in leukocytes. He died May 26, 1942.

The postmortem examination, as reported by Dr. Gustavus H. Klinck, Jr., at the Cluett Pathological Laboratory, Samaritan Hospital, Troy, N. Y., was as follows:

The body is that of an emaciated white man, 161 cm. in length. There is marked thoracic scoliosis to the right. As the body is turned much frothy, gray fluid flows from the mouth. The conjunctivae have a yellowish tint. The skin over the right thorax, anteriorly and posteriorly, is purplish brown, brawny, very adherent to the subcutaneous structures and in numerous places shows a delicate purple mottling.

The peritoneal cavity is free from fluid and adhesions. The diaphragm reaches to the level of the fifth intercostal space on the right and the sixth rib on the left. Pleural cavities are free from fluid. However, there is a thin film of sticky fibrin over the left lung causing adherence of most of the anterior and the greater part of the remaining surface of the lung to the pleura. A thick fibrous adhesion binds the extreme outer basal portion of the left lung to the diaphragm. The right lung is lightly attached to the chest wall posteriorly but the apex is firmly adherent. The pleura covering the anterior portion of this lung is thickened and has an opaque cobwebby appearance. The pleura over the posterior portion of the lower lobe, the middle lobe and the lower portion of the upper lobe is opaque, gray, wrinkled and measures about 1 mm. in thickness in its thickest portions. In the mediastinum there are a few very small but firm palpable nodes in the fat. Sections show small foci of glistening, grayish tissue. The pericardial cavity shows no significant change. The heart weighs 300 Gm. and appears enlarged, apparently due to dilatation of both ventricles, particularly the right. The epicardium and endocardium show no morbid change. The myocardium is flabby and



FIG. 5. Frontal section through middle of right lung. The white tumor mass is easily seen occluding the lower right bronchus just below its origin but extending upward as far as the carina tracheae. Peribronchial and perivascular extension has occurred. Elsewhere in the middle of the lower lobe there is much suppurative bronchitis with bronchiectasis. At the apex is a large collapsed bulla and in the peripheral zone of the right lobe bullous emphysema.

dark purple. The valve leaflets of both the tricuspid and mitral valves show small, nodular, rubbery thickenings along the edges. The chordae tendineae are shortened. The coronary arteries show a slight degree of thickening. The myocardium of the left ventricle measures 5 to 8 mm. The aorta shows a minimal degree of atherosclerosis.

Both lungs and trachea are removed and fixed by injecting formalin into the trachea according to the method of William Snow Miller and then suspending in Kaiserling I. Along the course of the right bronchus and at the bifurcation of the trachea are several reddish-gray and translucent, slightly firm lymph nodes, the largest of which is 3 by 1 by 1 cm. After fixation the lungs are re-examined.

The apex of the right lung has a very wrinkled appearance, apparently due to the presence of numerous cavities of collapsed bullae 1 to 2 cm. in diameter. The lung is further examined by

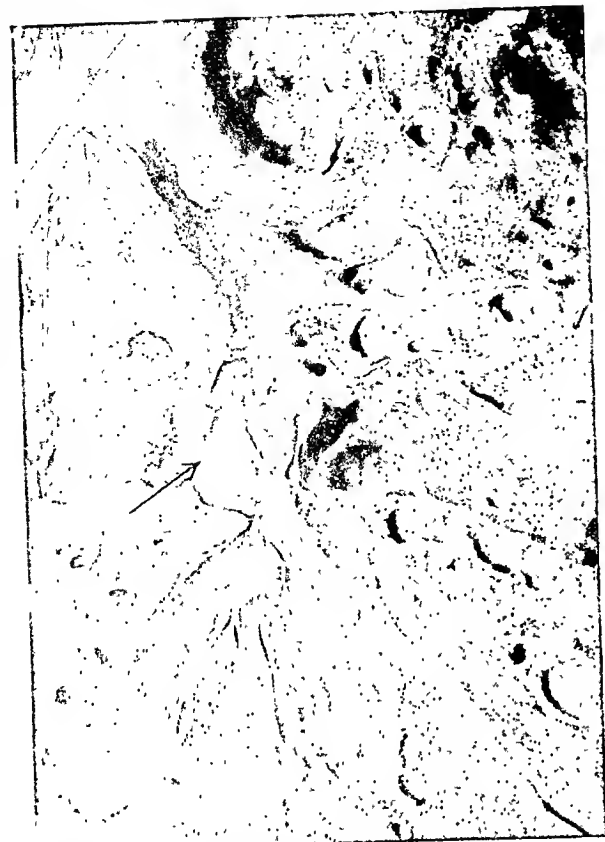


FIG. 6. An enlargement of the tumor-bearing area showing the occluding neoplasm with peribronchial extension and bronchiectasis.

making a single frontal section through the mid-portion. The section passes through the main bronchus. The branch to the lower lobe is apparently occluded by a grayish-white mass of dense, rather crumbly tissue, irregular in outline, unencapsulated and invasive. It measures 3 by 4 cm. in cross section. The branches of the bronchial tree of the lower lobe beyond this lesion show marked dilatation and their linings are rough and gray and contain puriform material. Near the obstructive lesion in the bronchus is a cavity about 2 cm. in diameter with a rough, nodular gray lining. In general the tissues of the lower lobe are moderately firm and retain some crepitation. Some portions, particularly the middle lobe, appear very fibrous on palpation. The upper portion of the upper lobe shows marked emphysema with cavities up to 1 cm. in diameter. A cyst-like space, 3 cm. in diameter, occupies the extreme apex. The cyst wall averages 2 mm. in thickness and has a gray lining that can be stripped away in layers. (Figs. 5, 6 and 7.) In the left lung a bulla 3 mm. in diameter is found at the apex. Many other



FIG. 7. Pleural surface of the right lung. Typical irradiation pleuritis, with pearly thickening and decrease in the normal wrinkling.

bullae 0.3 to 1.5 cm. in diameter are scattered in the subpleural zone of the median surface of the upper half of the lung but most of them are in the upper lobe. A paramedian incision discloses dense consolidation of the posterior half of the lower lobe becoming progressively less as the anterior portions of the lobe are approached. Thrombosis of several large blood vessels is found in the lower posterior portion. The upper lobe is soft and crepitant and shows all degrees of emphysema.

The spleen weighs 135 Gm. and is extremely soft. The capsule is smooth. Sections reveal purplish-brown tissue in which the usual markings are indistinct. The pancreas weighs 50 Gm. and is firm and pink. Parenchyma appears normal. The liver weighs 1,490 Gm. The capsule is smooth and thin. The consistence is about normal and the markings are distinct. The gall-bladder contains one rough, round cholesterol stone 1.5 cm. in diameter and about 20 cc. of thick, black bile. The adrenal glands are slightly enlarged and show postmortem softening. In

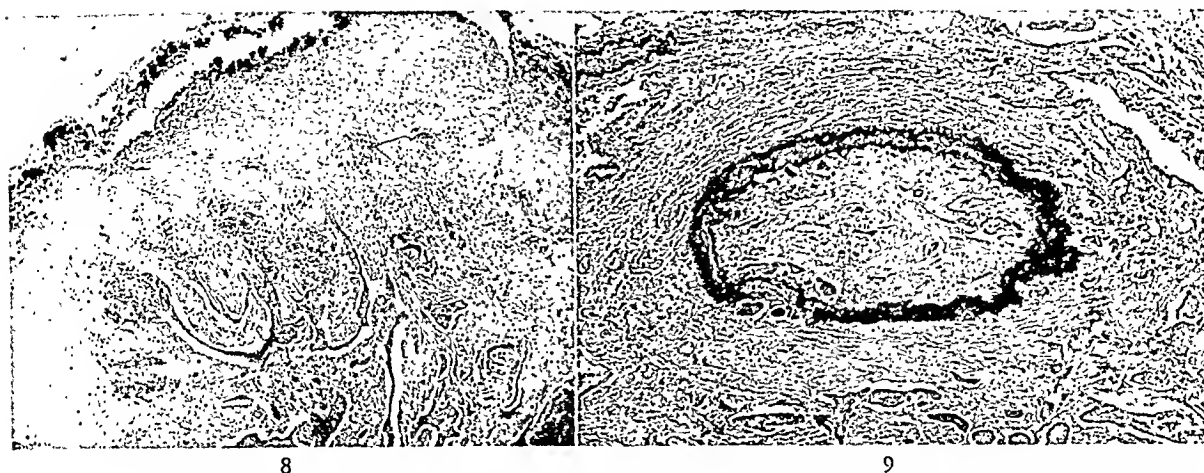


FIG. 8. A portion of the primary tumor projecting into the bronchial lumen. The wide zone of hyaline necrosis is a typical irradiation effect as well as the degenerative changes in the outlying groups of tumor cells. In the central core squamous epithelial cords with some keratinizing areas are still visible.

FIG. 9. A photomicrograph of a vein adjacent to the main tumor showing invasion of a thrombus, apparently from an area in the lower left segment where the elastica has been disrupted (Verhoeff's elastic tissue stain).

general the cortex averages 1 mm. in thickness and is firm and yellow. The medulla is soft, red and mushy. In the cortex of the right adrenal is an adenoma 6 mm. in diameter. The left kidney weighs 190 Gm. Its capsule strips off easily, revealing a smooth congested surface. Section reveals edema but otherwise normal markings. The right kidney weighs 155 Gm. and resembles the left kidney. The wall of the bladder is edematous and the mucosa shows foci of congestion. A soft reddish-yellow plaque 1 cm. in diameter is attached to the floor posterior to the trigone. The bone marrow of the vertebrae is soft and dark red.

Anatomical Diagnoses: Squamous cell carcinoma of the right primary bronchus; bronchopneumonia of the lower lobe of the right lung with bronchiectasis; pleural adhesions with hyaline pleuritis of the right lung; pleural adhesions and acute pleuritis of the left lung; valvulitis, chronic rheumatic, of the mitral and tricuspid valves; bullous emphysema of both lungs; dilatation of the heart; hypertrophy of the myocardium of the right ventricle; dilatation of the thoracic duct; cholelith of the gallbladder; papilloma of the urinary bladder; congestion, passive, of the kidneys; x-ray reaction of the skin of the thorax.

Microscopically, the thymus is represented by a mass of fat tissue containing a few widely spaced, spheroidal, calcareous deposits. In the heart there is slight separation of the perivascular and intermuscular fibrous tissue by edema. The intima of the aorta shows atherosclerotic thickening and the media contains some calcareous deposits.

Sections from the main branch to the lower lobe of the lungs reveal numerous anastomosing and isolated cords and masses of anaplastic epithelial cells of squamous type with occasional foci of keratinization. The tumor cells are variously supported by dense, hyaline, almost avascular fibrous tissue, recently formed fibrous tissue and necrotic tissue. Almost all sections show a border of granular necrotic tissue containing masses of bacteria. There is also necrosis of the bronchial wall in this area. In some parts the lung tissue is sclerosed and alveoli are lined by cuboidal cells. The more intact lung shows slightly to moderately thickened alveolar walls. Most of the alveoli contain many lipoid phagocytes. At points 4 to 5 cm. from the site of the neoplasm there is much parenchymal sclerosis. Some alveoli contain organizing exudate. At the base of the right lung there is fibrinous exudate covering a hyaline fibrous layer beneath which is a zone of telangiectasis. Some small veins in the region of the tumor are occluded by organized thrombi in which there are many cords of tumor cells that have disrupted the elastica by direct invasion. The left lung contains much air-containing tissue but in the lower lobe the alveoli are filled with leukocytic exudate, fibrin and edema fluid. Lymph nodes from the hila contain no tumor. (Figs. 8, 9 and 10.)

There is much hemosiderin in the spleen. The lymphoid follicles are small and few. In the pancreas one large duct shows squamous metaplasia of the columnar epithelium. The liver and adrenal glands show parenchymatous



FIG. 10. Pleura of irradiated lung showing fibrin overlying hyalinized connective tissue. Beneath this layer are numerous dilated capillaries in a loose framework containing many lymphocytes.

degeneration. The kidneys are normal except for marked congestion. A papilloma is present in the mucosa of the bladder. The lymph nodes from the thoracic and abdominal groups contain no tumor. A postmortem blood culture reveals no growth obtained after ten days of incubation.

COMMENTS

This case then is one of squamous cell carcinoma of a right primary bronchus with complicating bronchitis, bronchiectasis, pneumonitis and emphysema. The neoplasm was relatively small but because of its strategic location gave clinical symptoms over a period of nearly three years. During this long interval it remained within an area roughly 2 by 3 cm., grew slowly in the peribronchial tissues and even invaded regional veins which built up a protective thrombosis, again holding the tumor within a narrow hilar zone. It had not even emerged in the hilar lymph nodes. It was found nowhere else in the body.

Four months before death deep roentgen ray therapy was instituted, repeated bronchoscopic examinations up to that time having failed to reveal the neoplasm. This treatment was followed by a diminution of the cough reflex and a decrease in shadow at the base of the right lung. However, in this short time, as autopsy proved, several typical tissue reactions occurred that can be attributed to the action of the rays: (1) a hyalinizing pleuritis; (2) a vascularization of telangiectatic type in the subpleural

layer; (3) hyaline necrosis of the peripheral portions of the primary tumor.

The effects of the partial and finally complete obstruction of the bronchus by the tumor on the lung physiology were evident in the early dyspnea, cough, loss of strength, along with cyanosis and curving of the finger nails. These signs of anoxemia were far more pronounced than could be accounted for on the basis of lung tissue invaded by tumor, or pulmonary changes detectable by the usual methods of clinical examination, including x-ray studies. The entry of infecting organisms into the field supplied by the diseased bronchus provided an element practically always present in cases of bronchial carcinoma. The gradual development of bronchiectasis with focal bronchopneumonia deprived the patient of a large ventilating field as did the many emphysematous bullae.

Two series of deep x-ray treatments were given, totaling 10,400 r, divided among four portals. The postmortem evidence indicated a specific x-ray effect upon the pleura, subpleura, alveolar and vascular structures and very definitely upon the tumor itself. Hyaline necrosis of the peripheral zone of the tumor would seem to be a characteristic effect. The tumor was still viable in the central core but fragmentation of cells was occurring in the areas in which the dosage of rays was of sufficient depth. The tumor was of keratinizing type and hence somewhat radioresistant. The effect of the irradiation on the growth, then, was good as far as it went. The changes in the pleura and lung parenchyma were of course deleterious, and that poses the greatest problem in radiotherapy of tumors of the lung and elsewhere—how to destroy the tumor without seriously injuring the organ in which it grows.

Deep x-ray therapy of primary or secondary lung tumors is employed throughout the world where equipment and personnel are available. Radical lung surgery is successful in certain cases but too often one must be satisfied with such palliation as high voltage roentgen rays can offer.

But with all this clinical material, irradiation pulmonary or pleural fibrosis is not seen in every patient so treated. In 1925, Evans and Leucutia⁵ in eighty cases found the incidence rare unless repetition of large doses was necessary. Eighty per cent however, showed fibrosis if the dose exceeded 140 per cent of the skin unit dose, and they decided the lung changes were dependent on the quantity of radiation rather than on its wave length.

Desjardins⁶ in 1926 detected lung changes in only 2.5 per cent of several hundred cases in which the thorax received 800 to 1,000 r and never encountered it after 600 r. Age and arteriosclerosis were suggested as complicating factors. Lung vulnerability, according to Downs,⁷ was increased by acute and chronic infections and arteriosclerosis. McIntosh⁸ described four cases of pleuropulmonitis one to two months after irradiation of the thorax with accurate depth dose estimations, 2,000 to 4,000 r. Spencer and Warren⁹ believed that pulmonary metastases had no significant relation to the development of irradiation changes.

Widmann³ studied 273 cases of cancer of the breast in an effort to explain irradiation pulmonary fibrosis. He had used intensities of 1,600 to 2,000 r in one cycle, and 3,000 to 6,000 in two or more cycles (air) to each of three or four skin portals. In his series 22 per cent showed x-ray evidence of fibrosis and in 85 per cent of these there was metastatic lung cancer as proved at necropsy. Only 3.3 per cent of those alive three to ten years showed pulmonary fibrosis or, in other words, those clinically free from metastasis had the same incidence of irradiation changes as those with so-called normal lungs.

The mechanism of the dyspnea which invariably accompanies the pleura-lung fibrosis is not entirely clear, but Leach and his co-workers¹ believe there are at least four factors contributing: (1) a marked diminution of vital capacity because of the fibrosis itself; (2) fixity of the chest wall;

(3) compensatory emphysema; (4) hyper-irritable Hering-Breuer reflexes.

The most serious complications of a primary lung tumor are metastasis and bronchiectasis. This latter bronchial lesion may be due to partial obstruction of the bronchus by a papillary, polypoid or constrictive growth, or by a mass of granulation tissue or inspissated mucus superimposed along the mucosal tract. There are also effects of a reflex nature affecting the ventilating capacity of the lungs, but the intrabronchial suppuration and adjacent alveolitis contribute a massive focus of infection which is of major importance by adding to the mechanical respiratory problem a bacteriotoxic factor.

Intensive treatment of bronchiectasis is imperative in preserving life in patients with lung cancer. An excellent review of this subject up to 1941 is found in an article by Riggins¹⁰ who discussed the various medical measures of the time. Since x-ray therapy for bronchiectasis had been urged by Berck,¹¹ this modality was scrutinized critically and found unsatisfactory. Lobectomy or pneumonectomy was advised by Riggins for suitable patients in the hands of experienced thoracic surgeons. In the case here reported there was no evidence of a favorable effect upon the bronchiectasis of the two courses of deep x-ray irradiation. In controlling the bacterial flora, penicillin, streptomycin, and the sulfonamides have found an important place in the modern treatment of chronic bronchial infections and should be employed early in the management of primary or secondary lung cancer.

SUMMARY

1. Cancer of the lung endangers life by reason of (1) its location with reference to large bronchial trunks; (2) the rapidity of growth of the primary lesion; (3) its metastatic spread; (4) the high incidence of pulmonary infection, usually with some degree of bronchiectasis.

2. A case is presented of a relatively small squamous cell carcinoma of the

lower right bronchus, arising near the hilum and causing marked bronchiectasis and pneumonitis. Deep x-ray therapy effectively prevented spread of the tumor from a narrow hilar zone but injured the pleura and lung parenchyma.

3. While some roentgenologists have employed deep x-ray technic in the treatment of bronchiectasis, there was no evidence of a favourable influence on this complication of the two courses of x-ray exposures totalling 10,400 r.

4. Since pulmonary infection is an almost constant finding in patients with lung cancer, intensive treatment with penicillin and/or sulfonamides or streptomycin should be the rule, whether or not radical surgery or deep x-ray therapy is employed. This might at least improve the patient's general condition and thus add to his life expectancy as well as make him a better operative risk.

5. There is need for further refinements in the control of high voltage roentgen therapy of cancer of the lung in order to

prevent harmful reactions in normal pleura and lung parenchyma.

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American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EASTERN SECTIONAL MEETING HELD IN NEW YORK,
DECEMBER 12, 1947

FAMILIAL IDIOPATHIC DYSPROTEINEMIA. I. CLINICAL DESCRIPTION OF A NEW SYNDROME. *F. Homburger, M.D., New York, New York.* (From the Sloan Kettering Institute for Cancer Research.)

A new syndrome, familial idiopathic dysproteinemia, was found in a mother, four of her adult children and two of her grandchildren. The syndrome is characterized by hypoproteinemia and/or changes in the electrophoretic plasma protein patterns, by peripheral vascular disturbances (low oscillometric indices in the females, ulcers of the legs in the males) and by anomalies of the thoracic cage.

In one case protein metabolism was studied and it was found that no regeneration of plasma protein occurred while the patient was in positive nitrogen balance. Plasma protein was readily mobilized to replace small amounts of protein acutely withdrawn by plasmapheresis. Injected albumin disappeared from the circulation at the same rate as in a normal control subject. The disappearance rate of injected γ -globulin, however, was rapid and antibody formation (isohemagglutinins and pneumococcus polysaccharide antibodies) was defective. These findings demonstrate the complexity of the homeostasis of plasma proteins and suggest the existence of hereditary factors governing these mechanisms.

STUDIES IN COPPER METABOLISM IN PATIENTS WITH MELANOMA. *J. B. Trunnell, M.D., A. H. Minor, M.D. and N. F. Young, Ph.D., New York, New York.* (From the Sloan Kettering Institute for Cancer Research.)

Because melanoma tissue has been shown to contain concentrations of copper second only to the liver, studies have been undertaken to assess the possibility of significant intracellular radiation therapy with radioactive copper. Cu^{64} and

Cu^{64} have been employed in a patient with metastatic melanoma. Observed were: (1) Rapid disappearance of intravenously administered copper from the circulation, followed by reappearance after about two hours increasing up to twenty hours; (2) rapid appearance in the liver and bile; (3) low total urinary and fecal loss; (4) slow and scant concentration in melanoma tissue.

In a second patient efforts were made to create copper deficiency prior to administration of Cu^{64} so that pick-up by melanoma might be increased.

BAL was found to increase the urinary excretion of copper by a factor of three. Prolonged administration of BAL during a period of low copper intake (di-thio-carbamate used for copper determinations) was found not to mobilize copper from the body, probably because it appears to be metabolized.

RÔLE OF BILE IN THE ABSORPTION OF STEROIDS FROM THE GASTROINTESTINAL TRACT. *M. M. Hoffman, M.D., Montreal, Canada.* (From the McGill University Clinic, Royal Victoria Hospital.)

Since bile is required for the optimum absorption of cholesterol from the gastrointestinal tract, it has been assumed that bile is also essential for enteral absorption of steroid hormones and related substances. On this assumption, bile salts have been administered simultaneously with steroid hormones to patients and experimental animals in an endeavor to enhance the effectiveness of the latter substances. To determine if this assumption is correct effect of the absence of bile from the gastrointestinal tract on the absorption of steroid hormones was studied. Dehydroisoandrosterone, progesterone and desoxycorticoesterone acetate were individually administered by gavage to normal rabbits and to rabbits in which the bile ducts had been ligated. In each

instance the amounts of metabolites excreted in the urine of the normal animals were compared with the amounts excreted by the animals with ligated bile ducts. It was found that following administration of dehydroisoandrosterone to animals in which bile was absent from the gastrointestinal tract, the amounts of 17-ketosteroids in the urine were equal to those excreted by the normal animals similarly treated. Pregnanediol glucuronide was excreted in the urine following administration of progesterone and desoxycorticosterone acetate to the animals with ligated bile ducts. It is therefore concluded that absorption from the gastrointestinal tract of dehydroisoandrosterone, progesterone and desoxycorticosterone acetate can take place in the absence of bile.

ADRENAL CORTEX RESPONSIVENESS TEST:

EVALUATION OF RESULTS IN GASTRIC CANCER. *Edward C. Reifenstein, M.D., F. Homburger, M.D., N. F. Young, Ph.D. and Aurelia Potor, M.D., New York, New York.* (From the Department of Clinical Investigation of the Sloan-Kettering Institute, Memorial Hospital Cancer Center.)

Injection of anterior pituitary adrenocorticotrophic hormone induces a fall in the blood eosinophile level and a rise in the urinary uric acid/creatinine ratio in persons with normally responsive adrenal cortices. Because of evidence suggesting that patients with cancer may have disordered function of the adrenal cortex, this test has been applied to patients with gastric cancer. Preliminary results (fifteen patients) indicate that although adrenocorticotrophic hormone in the dosage used induces the expected fall in the eosinophile level, it produces no significant change in the uric acid/creatinine ratio in the majority of these patients. The most striking finding is the discrepancy between these two responses. It remains to be determined whether or not the adrenal cortical mechanism for regulating urinary uric acid/creatinine ratio in these patients is unresponsive to pituitary trophic hormone stimulation because it is less sensitive or because it is functioning at the limit of its capacity.

FACTORS INFLUENCING THE EOSINOPHILE CONTENT OF NASAL SECRETION. *Thomas H. Holmes, M.D. and Helen Goodell, B.S., New York, New York.* (From the New York

Hospital and the Department of Medicine, Cornell University Medical College.)

Eosinophile counts of nasal secretions in a group of twenty-five subjects were made. Fresh, wet nasal mucus was mixed in a test tube with a small amount of Hastings' stain and was mechanically agitated for two minutes with a stirring rod. The occurrence of 1 per cent eosinophiles in the total count of cells was considered significant. An increase in the eosinophile content of nasal secretions accompanying hyperemia, engorgement, hypersecretion and obstruction in the nose occurred in response to the following threats: (1) Specific threats, i.e., chemical agents, infectious agents and pollens directed at the nasal mucous membrane. (2) A specific threat directed at parts of the head other than the nose, i.e., noxious stimulation by a tight band inducing head pain. (3) General threats to bodily function, i.e., life situations evoking resentment.

Presence of increased numbers of eosinophiles in the nasal secretions together with hyperemia, engorgement, hypersecretion and obstruction apparently constitute a part of the protective pattern of shutting out and washing away agents noxious to the nasal mucosae as well as other threats and assaults directed against the integrity of the individual.

METABOLIC STUDIES ON A CASE OF ACROMEGALY WITH SPONTANEOUS DISAPPEARANCE OF DIABETES MELLITUS. *T. P. Almy, M.D. and Ephraim Shorr, M.D., New York, New York.* (From the Russell Sage Institute of Pathology, the Department of Medicine, Cornell University Medical College, and the New York Hospital.)

A patient who had typical acromegaly for fourteen years and severe diabetes mellitus for five years became suddenly ill with otitis media, mastoiditis and basilar meningitis. During this illness glycosuria and hyperglycemia completely disappeared and have not reappeared during a five and one-half-year period of follow-up. There were associated changes in somatic growth disturbances, gonadal function and basal metabolism, suggesting that the patient had suffered damage to the anterior pituitary. Metabolic study conducted five years after disappearance of the diabetes indicates that the patient can now produce insulin and metabolize glucose in approximately normal amounts.

Appearance and disappearance of diabetes in this patient, apparently attributable to disturbances in the anterior pituitary, are considered in the light of our growing experimental knowledge of the rôle of the pituitary in carbohydrate metabolism.

NEW CONCEPT OF TRAUMATIC DIABETES.

*A. J. Kauvar, M.D. and (by invitation)
M. G. Goldner M.D. Ft. Logan, Colorado.*
(From the University of Colorado School of Medicine and Veterans Hospital.)

Diabetes is now recognized as being traumatic in origin only when it develops following direct injury to the pancreas. Modern physiology has shown that the body reacts to trauma with a general metabolic response and it becomes more and more evident that the "alarm reaction" is of as great clinical importance as is the locally sustained traumatic injury. Carbohydrate metabolism has been found to be involved intimately in adaptation of the organism to the traumatic reaction.

The purpose of this presentation is to relate a series of clinical observations in which a diabetic syndrome developed abruptly in connection with sudden severe illness (coronary occlusion, pulmonary embolism, abdominal surgery, septicemia, fracture of femur). An attempt is made to interpret the pathogenesis in these cases on the basis of a functional disturbance of the metabolic response to an emergency situation, rather than as the result of primary organic disease of the pancreas.

In only two cases could diabetic heredity be established. In all instances the onset of the disease was severe, requiring vigorous insulin treatment. Ketosis was present in two cases. With improvement of the precipitating disease, the diabetes showed marked amelioration.

Since the modern concept of trauma comprises not only local reaction to injury but the bodily response as well, it is proposed to broaden the concept of traumatic diabetes to include recognition of the alarm reaction as an etiologic mechanism.

EXPERIMENTAL STUDY OF THE LIFE SITUATIONS, EMOTIONS AND THE OCCURRENCE OF ACIDOSIS IN A JUVENILE DIABETIC. *Lawrence E. Hinkle, Jr., M.D. and Stewart Wolfe, M.D., New York, New York.* (From the New York Hospital and the Depart-

ments of Medicine and Psychiatry, Cornell University Medical College.)

Clinical experience in the past has suggested that the course of diabetes mellitus can be influenced by life situations which induce certain emotional changes in the patient. Substantiation of this depends upon direct correlation of changes in the metabolic state with emotional states in diabetic subjects. The present report concerns such a detailed study in the case of a fifteen year old school girl who, despite careful regulation of insulin dosage and dietary intake, recurrently became acetonuric and required admission to the hospital twelve times within a period of five years.

She was found to be anxious, insecure and in constant conflict with her tyrannical mother. During one hundred days of observation it was found that she developed ketonuria on nine occasions, immediately after the onset of a situation which produced intense anger or fear. There were only nine such situations during the observation period and all were followed by ketonuria.

Further control of the experimental situation was achieved during a period of ten days when the patient was hospitalized and subjected to rigid control of dietary intake, insulin and muscular activity. Following a suitable control observation in the setting of a major threat to her personal security, she became intensely frightened and angry. Ketonuria appeared within twelve hours, was sustained throughout the period of stress and finally disappeared after the reassurance and reestablishment of security.

Thus alteration in the carbohydrate and fat metabolism as manifest by development of ketonuria appeared to be directly related to the emotional state and security of the subject.

SICKLING IN NEGRO NEWBORNS: ITS POSSIBLE RELATIONSHIP TO FETAL HEMOGLOBIN. *Janet Watson, M.D., Brooklyn, New York.*

Sickling preparations were made in 226 consecutive newborn negro infants and their 226 mothers. The standard sealed slide preparation incubated at 37°C. was used. Of the 226 infants, nineteen or 8.4 per cent showed sicklemlia; of the 226 mothers, eighteen or 8.0 per cent showed sicklemlia. Although the incidence of sicklemlia was almost identical in the two series, two differences in regard to the sickling became

evident: First, a time interval of forty-eight hours was often required for maximum sickling of the infants' red cells in contrast to the twenty-four-hour period necessary for the mothers' cells. Secondly, the infants' red cells showed only 0.5 to 29.5 per cent sickling while the mothers' cells showed 84 to 100 per cent sickling.

Fetal hemoglobin differs chemically from adult hemoglobin in several respects and, as tested by the alkali denaturation method, does not disappear from infants' blood until the age of four and one-half months. It is interesting that one of our patients with sickle cell anemia followed from birth developed progressively increased sickling from 6 per cent at birth to 90 per cent at four and one-half months. This is also correlated with the estimated four-month life span of the erythrocyte. In view of these data it is suggested that the low percentage of sickling in newborns is due to the presence of fetal hemoglobin, and that this fetal hemoglobin accounts for the absence of death from sickle cell disease *in utero* where the low oxygen tension would otherwise cause sickling with the usual disastrous pathologic sequelae.

SENSITIVITY OF THE TUBERCLE BACILLUS TO STREPTOMYCIN BEFORE AND DURING THERAPY OF PULMONARY TUBERCULOSIS. *Joseph F. Sadusk, Jr., M.D. and (by invitation) William E. Swift, Jr., M.D., New Haven, Connecticut.* (From the Department of Internal Medicine, Yale University School of Medicine.)

In vitro sensitivity of tubercle bacilli isolated from sputa or gastric contents was determined in a group of sixteen patients with pulmonary tuberculosis receiving 1.8 Gm. of streptomycin daily for a period of four months. *In vitro* tests were performed in Dubos medium.

In all sixteen cases the strains of bacilli isolated prior to treatment were highly sensitive to streptomycin. Fourteen of these sixteen strains were inhibited by 0.5 microgram of streptomycin per ml., the remaining two strains were inhibited by 1.0 microgram per ml. Loss of sensitivity (ten-fold increase in resistance) began to appear by the end of the first month of therapy together with conversion of positive sputum or gastric washings to negative in other cases as determined by culture. By the end of the third and fourth months of therapy cultures were positive in only nine of the sixteen patients.

Tests of organisms from these nine positive cultures indicated that all of them had developed a ten-fold or greater increase in resistance. Five of these nine strains developed a ten to fifty-fold increase in resistance; the remaining four strains developed a 100 to greater than 2,000-fold increase in resistance.

It was not possible with this small group of patients to demonstrate conclusively a correlation between resistance to streptomycin and the clinical course under therapy.

TREATMENT OF PNEUMOCOCCIC MENINGITIS BY SYSTEMIC PENICILLIN. *H. F. Dowling, M.D., L. K. Sweet, M.D. and H. L. Hirsh, M.D., Washington, D. C.*

When penicillin is employed in addition to sulfonamides, the fatality rate in pneumococcic meningitis is reduced below that obtained with sulfonamides alone. Nevertheless, results obtained up to the present are far from satisfactory. According to accepted methods of treatment, penicillin is given intrathecally in amounts of 10,000 to 20,000 units per day and systemically in doses of about 500,000 units a day with full doses of sulfadiazine or sulfamerazine systemically.

Intrathecal administration of penicillin possesses many disadvantages. Among these are: (1) The possibility of radiculitis or convulsions developing when large amounts are given or when concentration of penicillin in the cerebrospinal fluid reaches high levels; (2) irritative action of penicillin upon the meninges, evidenced by development of pleocytosis and the possibility that this may cause adhesions and block; (3) difficulty and danger of repeated lumbar punctures. Intrathecal penicillin is employed because many investigators have failed to find demonstrable amounts of penicillin in the cerebrospinal fluid after systemic administration. Others have shown, however, that when sufficiently large doses of penicillin are given systemically, therapeutic levels are consistently obtained in the cerebrospinal fluid.

After preliminary studies had demonstrated that a therapeutic concentration of penicillin was consistently present in the cerebrospinal fluid of subjects receiving 1,000,000 units of penicillin intramuscularly every two hours we administered this dose plus sulfadiazine and sulfamerazine to patients with pneumococcic meningitis. Two patients received one intrathecal dose of penicillin; six received none. Five

patients recovered and three (37.5 per cent) died. In all fatal cases death occurred within twelve hours of the first dose of penicillin. All the patients who died were in unfavorable age groups and had been ill for some time before admission to the hospital. Among fifty-three patients treated by us with smaller amounts of systemic, plus daily intrathecal penicillin, 60 per cent died, and fever and pleocytosis were more prolonged than in those patients given no intrathecal penicillin or only given a single dose. Clinical and laboratory observations on the patients in the two groups are compared.

ENZYME INHIBITION BY ALPHA-TOCOPHEROL PHOSPHATE: EFFECT ON CERTAIN RESPIRATORY AND PROTEOLYTIC SYSTEMS AND ON BLOOD COAGULATION. *K. L. Zierler, M.D. and (by invitation) D. Grob, M.D. and J. L. Lilienthal, Jr., M.D., Baltimore, Maryland.* (From the Physiological Division, Department of Medicine, Johns Hopkins University and Hospital.)

Alpha-tocopherol phosphate (α -TPh) slows the accelerated oxidative processes in muscle dystrophy associated with vitamin E deficiency. α -TPh, *in vitro*, inhibits the succinoxidase system. In an effort to elucidate the mechanism of inhibition, studies were undertaken concerning the effect of α -TPh upon a number of enzyme systems. The systems were selected because they shared with the succinoxidase system a requirement for ionic calcium or because they contained sulfhydryl enzymes. (1) The adenosinetriphosphatase system was not influenced by α -TPh when optimal calcium concentration was maintained. (2) Coagulation of recalcified human plasma was prevented by α -TPh even when the molar ratio of ionic calcium to α -TPh was 10:1. Furthermore, as little as 10^{-8} M of α -TPh inhibited clotting of a thrombin-fibrinogen system. (3) α -TPh slightly inhibited the sulfhydryl enzyme papain. α -TPh inhibited trypsin, plasma protease and leuko-protease as effectively as did the specific antiproteases.

When α -tocopherol phosphate was injected into normal rats, large doses uniformly produced apparent drowsiness, ataxia and weakness; occasionally, convulsions and death. When the animals were sacrificed during the period of "drowsiness," succinoxidase activity of muscle and of brain was normal. Oxygen consumption

of the diaphragm in Ringer-phosphate solution, however, was reduced while that of the brain was normal.

α -TPh, therefore, is anti-oxidative, anticoagulant and antiproteolytic.

DYSTROPHICA MYOTONIA. *C. S. Nadler, M.D., Manrico Troncelletti, M.D. and (by invitation) William Steiger, M.D. and Thomas M. Durant, M.D., Philadelphia, Pennsylvania.*

The present studies confirm Waring's concept of dystrophica myotonia, i.e., it is a heredo-generative disease, predominated by a modified Mendelian dominant gene. This is further modified by a type of mutation which is exhibited by progressive inheritance.

Dystrophica myotonia patients present the endocrine features of a specific type of hypogonadism. This is described by and called "Klinefelter's syndrome" which is characterized by small testes, aspermatogenesis, increased excretion of follicle-stimulating hormones and decreased excretion of 17-ketosteroids. Our patients also were compatible with Heller and Nelson's modification of this syndrome, i.e., "Leydig cell failure." Autopsy of one male patient with dystrophica myotonia showed, in addition to hyalinization of the seminiferous tubules, a decrease in the size of the adrenal and thyroid gland. Participation of the latter glands in the etiology of dystrophica myotonia and Klinefelter's syndrome is discussed. The beneficial effect of large doses of testosterone propionate in males is described.

Thus clinical and laboratory evidence seems to indicate that the etiology of dystrophica myotonia is that of defective genes which, through an evolution of status degenerans, cause secondary changes. These changes characteristically affect the lens of the eye, the muscular, vascular and endocrine systems.

EFFECT OF CHRONIC POISONING WITH DI-ISOPROPYL FLUOROPHOSPHATE ON NEUR-MUSCULAR FUNCTION IN THE CAT. *Carlton C. Hunt, M.D. and Walter F. Riker, M.D., New York, New York.* (From the Department of Pharmacology, Cornell University Medical College.)

Di-isopropyl fluorophosphate (DFP) has been shown to inactivate irreversibly serum and tissue cholinesterase. Following large doses of DFP,

cats developed a protracted syndrome of muscular weakness lasting as long as five months. In the present study effects of repeated large doses of DFP in the cat were studied by symptomatology, neuromuscular function and cholinesterase activity of nervous and muscle tissue.

Cats which had received from two to six (average of four) daily intramuscular injections of 1 mg./kg. of DFP in oil showed ataxia, extreme muscular weakness and generalized fasciculations. Following the disappearance of fasciculations on the third to fourth day after poisoning, the animals showed generalized weakness and fatigability. Subsequent to this recurrence of the weakness developed which was chiefly confined to the hind limbs and which lasted from 21 to 147 days.

At varying intervals after poisoning the response of the muscle to intra-arterial injection of acetylcholine and the response to nerve stimulation was studied. Increased sensitivity to acetylcholine was present (one to ten days) and a prolongation of the contractile response (four to eighteen days) resembling that seen after denervation. The muscle was unable to maintain a tetanus induced by indirect stimulation (one to six days). Regeneration of muscle cholinesterase activity was complete in two weeks. By one month the brain cholinesterase had reached 69 per cent and the nerve 85 per cent of their control values.

It is concluded that the syndrome described results from extreme reduction of muscle and nervous tissue cholinesterase by DFP. Changes in the response of the muscle to acetylcholine following protracted inactivation of cholinesterase suggest the development of an injury at the myoneural junction resembling that associated with denervation.

OBSERVATIONS ON SPREAD OF PAIN. *E. Charles Kunkle, M.D., George C. Armistead, M.D. and Helen Goodell, B.S., New York, New York.* (From the New York Hospital and the Department of Medicine, Cornell University Medical College.)

The digits of the hand as distinct projections of the body are particularly suitable for the study of spread of pain from a site of noxious stimulation. An effective and reproducible stimulus has been found in the immersion of a

finger in water maintained at 0°C. Pain thus induced follows a conveniently cyclic course.

In one hundred experiments upon twenty-two adult subjects "cold" pain was nearly always found to overflow to adjacent areas, notably to neighboring digits. Features common to this phenomenon in almost all of the experiments were a "latent" period, "facilitation" in subsequent phases of the pain cycle, "tapering" of intensity and "incomplete segmental filling." The direction of spread was predominantly caudad in most instances. In no subject was contralateral extension of pain noted. Pain failed to spread from thumb to jaw (in cortical sequence). Overflow of pain was unaltered by preliminary interruption of the circulation to the arm or by procainization of an area into which spread of pain was to occur.

In contrast to these typical features of spreading pain, other and less "orderly" characteristics were noted. Most prominent was the moderate intraindividual and marked interindividual variation in extent of spread. In a minority of instances the spreading pain "migrated" during the experiment, "skipped" a digit or reached a higher intensity than that of the primary pain ("insubordination").

Many of these listed features of spreading pain have also been observed in patients with traumatic digital lesions, dental disease or angina pectoris. It is inferred that such overflow of pain is a central phenomenon and probably occurs at the segmental level in the cord. This mechanism contrasts sharply with spread of pain due to a peripheral effect, as in secondary contraction of skeletal muscle, and with reference of pain throughout the domain of a sensory nerve trunk as the result of a proximal nerve or dorsal root lesion.

EXPERIMENTAL STUDIES ON THE NATURE OF HYPERALGESIA. *H. G. Wolff, M.D., J. D. Hardy, M.D. and H. Goodell, B.S., New York, New York.* (From the New York Hospital and the Departments of Physiology, Medicine and Psychiatry, Cornell University Medical College.)

There are a number of varieties of hyperalgesia. Considered here is that which can be experimentally induced in areas of skin adjacent to sites of noxious stimulation as described by Sir Thomas Lewis. In these areas pain threshold is not lowered although pin pricks and thermal

stimuli above the pain threshold elicit more intense and longer lasting painful sensations than in control areas. Hyperalgesia develops from tissue injury in a procainized skin area as soon as the procaine effect begins to diminish. After hyperalgesia has become established complete procainization of the site of injury immediately eliminates hyperalgesia. Also the rate of development and spread, as well as elimination of the hyperalgesia by injection of procaine, are unaffected by occlusion of blood supply. Hyperalgesia develops in areas adjacent to prolonged thermal radiation inducing no more than threshold to minimal pain, and hyperalgesia does not persist longer than the stimulation. Pin pricks in the zone of hyperalgesia cause the minimal pain from the site of noxious stimulation to be intensified. These observations make it difficult to explain this type of hyperalgesia either on the basis of local liberation of a humoral substance in the site of hyperalgesia or a special nocifensor system as postulated by Lewis. On the basis of the aforementioned evidence it is suggested that hyperalgesia in areas adjacent to a site of noxious stimulation of the skin is dependent upon spread of a central excitatory state which results from a sustained barrage of noxious impulses from the periphery.

INTRA-OCULAR PRESSURE VARIATIONS IN GLAUCOMA ASSOCIATED WITH EMOTIONAL CHANGES. *Herbert S. Ripley, M.D., New York, New York.* (From the New York Hospital and the Departments of Medicine, Psychiatry and Surgery (Ophthalmology), Cornell University Medical College.)

In view of the long held opinion that personality factors play a part in the etiology or precipitation of attacks of glaucoma a study was undertaken in order to determine whether or not there was a relationship between emotional reactions and the level of intra-ocular pressure. Data concerning life history, eye symptoms and intra-ocular pressure were gathered on twelve patients with primary glaucoma. During interviews intra-ocular pressure and blood pressure were recorded.

Personality studies revealed a high incidence of the following characteristics: resentment, anxiety, moodiness, inordinate body preoccupation, conscientiousness, meticulousness, difficulty

in maintaining satisfactory interpersonal relationships and sexual maladjustment.

Positive correlations were noted between development of a variety of difficult life situations and the presence of eye symptoms. During interviews, both with and without intravenously administered sodium amytal, fluctuations in intra-ocular pressure were found to be associated with psychodynamic factors and emotional variations. Conscious and unconscious psychic reactions, which appeared to disturb the balance between the sympathetic and parasympathetic nervous systems, resulted in both widespread vasomotor responses involving the systemic blood pressure and in localized reactions in the eyes. Elevations of intra-ocular pressure were associated with such varied emotions as anger, anxiety and depression. During periods of emotional calm, satisfaction or happiness lower intra-ocular pressures were obtained.

In one patient treated with personality analysis, explanation and reassurance there was simultaneous improvement in intra-ocular pressure and anxiety. This suggests that psychotherapy may have value in management of patients with primary glaucoma.

STUDIES IN EPILEPSY. *Wayne Barker, M.D. and Stewart Wolf, M.D., New York, New York.*

The relationship between convulsive symptoms and aggressive urges has been frequently discussed but the exact nature of the relationship has not been clarified. Sodium amytal interviews have been used to clarify the relationship between life problems and symptoms in other disorders. The relevance of certain situations and conflicts to the patient's disordered bodily function has been observed by means of changes in the intensity of symptoms which occur with changes in the content of such interviews.

This study was undertaken to ascertain, in similar fashion, the relationship between the pertinent problems and symptoms of an epileptic patient. The technic of electro-encephalography during sodium amytal interviews was used.

The patient's life history was characterized by a severe conflict between intense aggressive urges and strong needs for love and affection. Major convulsions and psychomotor seizures frequently occurred in situations in which aggressive wishes were aroused but were blocked by the situational circumstances. Clinical study and EEG confirmed the diagnosis of "epilepsy."

Under light sodium amytal narcosis (Gm. 0.3) the patient reacted an episode in which love and hate for his mother were in sharp conflict. An increasingly violent and intense state of rage culminated in an attack of grand mal clinically, and electro-encephalographically characteristic. The fit appeared to resolve, in a dynamic sense, the conflict between uncontrollable rage and the restrictions of conscience and society. The rôle of sodium amytal in the genesis of the reaction is discussed in terms of inactivation of cortical inhibitory influences.

ACTION OF NEOSTIGMIN IN SUPRAVENTRICULAR TACHYCARDIAS. *Samuel Waldman, M.D. and Louis Pelner, M.D., Brooklyn, New York.*

Supraventricular tachycardias of sinus, auricular and nodal origin can be successfully treated by the administration of 1 mg. of neostigmin methylsulfate intramuscularly. Action of this drug is predicated in these instances by its stimulating effect on the vagus nerve. Stimulation of the right vagus is the predominant factor in sinus tachycardia since this nerve ends especially at the sino-auricular node in which the disturbance originates, correction of which restores normal sinus rhythm. That this occurs is borne out by electrocardiographic studies on patients in whom the effect noted is a slowing of the heart by a decrease in rate of impulse formation at the sinoauricular node. An increased T-P interval is produced.

In the case of paroxysmal auricular and nodal tachycardias, stimulation of the right vagus would not correct this defect since the defect is not at the sino-auricular node. We could expect left vagal action to be effective since those fibers terminate mainly at the auriculoventricular node. Stimulation here would produce inhibition of conductivity and then induce a heart block of varying degree depending upon the extent of diminished conductivity. That this actually occurs is shown by electrocardiographic studies in those patients in whom heart block occurs varying from first degree block with increased P-R intervals to 2:1, 3:1 and 4:1 incomplete block. No case of complete block was found. After the block normal sinus rhythm was restored.

DIAGNOSTIC AND THERAPEUTIC USE OF TETRAETHYLAMMONIUM AND DIBENAMINE.
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The effects of tetraethylammonium and dibenamine have been investigated in ninety-six patients with perivascular disease and hypertension. The beneficial effects of these drugs are dependent entirely upon the temporary vasomotor paralysis which they produce, and unless we assume that they have some additional beneficial action (which, as yet, has not been demonstrated) they can be only as effective as any other measure which produces a similar degree of vasomotor paralysis.

The physiologic state produced by sympathectomy differs markedly from that produced by temporary vasomotor paralysis regardless of how the paralysis is achieved. Temporary vasomotor paralysis, therefore, does not uniformly predict the results of sympathectomy in treatment save in some acute occlusions. Since the blockade produced by tetraethylammonium varies in extent and degree, it has been found even less reliable than paravertebral sympathetic block in predicting the results of sympathectomy in perivascular disease. Dibenamine, because it produces a block which may last from twelve to ninety-six hours, may be superior to other diagnostic tests in selecting patients with obliterative disorders for sympathectomy. Neither drug in our experience has proved to be of value in selection of hypertensive patients for sympathectomy.

In the treatment of acute vascular occlusions, temporary vasomotor paralysis may be of great value. Tetraethylammonium and dibenamine are both useful, but we prefer dibenamine because of the longer duration of action. In the chronic perivascular disorders the value of temporary vasomotor paralysis must yet be proved. Tetraethylammonium and dibenamine have not proved to be of greater value than other similar methods of treatment. It is doubtful that either drug is appropriate in the treatment of hypertension.

Editorial

Problems of Convalescence

ACCORDING to Stedman's Medical Dictionary the word convalescence (growing strong) refers to the time that elapses between the termination of a disease and the patient's complete restoration to health. The simple finality of that statement invites discussion. Its implied supposition that "a disease" is something a man "gets" or "has" maintains the primitive concept that he himself is a victim of olympian wrath. That he may be an important causal factor in his own malady the statement completely overlooks. One might as well ask when does a disease actually begin as to judge when it terminates. The pathologic events which occur between two successive states of health form a continuum. The course or curve in recovery from the onset of disease to the stated cure varies greatly with different persons. In some cases the curves of disease from onset to peak and through the descent are rapidly described. In others every variation in form and speed appears. Those who dally in regaining health and in the ability to return to their previous life-setting deserve special scrutiny. No doubt various facts and motives determine why slow recoverers are slow. Of course, many subjects with early deterioration of tissues such as liver, kidney or arteries, as well as those with rheumatoid arthritis and similar disabilities, should hardly be classed as convalescents. They clearly belong in the growing ranks of victims of chronic disease whose chances for ultimate recovery are what they may be. A good deal can often be done to make resumption of work fairly successful for

shorter or longer periods of time. This type of fixed tissue disease rarely moves in the direction of biologic recovery. But even with great physical handicaps certain persons may achieve superb capacity for work. Deaver, Rusk and others have shown that the patients' effectiveness may be maintained for remarkably long periods by proper, diet training and point of view.

In many convalescent homes the most satisfactory patients, as far as recovery is concerned, are those whose maladies arise in the organs equipped with smooth muscle which is motivated by the autonomic nervous system. These include the whole field of the neuroses, for example, peptic ulcer, thyroid disease, asthma, enteritis and essential hypertension.

In Homeric times the Greeks used to speak of two varieties of medicine—profane and sacred. The former dealt with sewing up the wounds of a warrior, setting broken bones and treating any ailment caused by explainable physical forces. Sacred medicine or magic, on the other hand, had to be called upon for maladies whose concealed inner mechanism could not be perceived or directly dealt with by tangible methods. The former has come down the ages to end in modern surgery and physiotherapy for physical rehabilitation. Sacred medicine or magic has turned into contemporary psychotherapy. Today the combined techniques are expressed in that presently overworked word, "psychosomatic."

And this brings us to the specific problems of convalescence and convalescent care. The question has often been raised

as to what sort of regimen should be provided at convalescent homes. In the first place, the term "home" carries a maternal connotation of "being taken care of," a continuation of the protective nursing just terminated in the general hospital. If the patient is well enough to leave that phase of his illness, he should be weaned as promptly as possible. A better name for the modern convalescent home would be "Recovery Training Institute." The effort of all concerned with the patient's ultimate recovery should be to help him as little and as indirectly as possible within the limits of good sense. One of the remarkable achievements at the Bellevue Clinic has been the education of patients to help themselves and to become independent of their former aids. They are taught self-sufficiency in the face of handicaps.

There are times, too, when patients flee from apparently insoluble family troubles "just to get away from it all." Such cases derive scant benefit from the three weeks of sunlit and well fed loneliness among strangers, agoraphobia and anticipated terror at the idea of returning to their unsolved problems. These individuals might better have settled the home conflict first. It probably led to the acute illness or general collapse which called for a convalescent period. After such a settlement the healing virtues of fresh air, sunshine, good food and rest might have produced more rapid and complete rehabilitation. The recovering patient is in a tough spot indeed, one which often defies a first-class social service worker. A large number of patients who avoid the guidance of a well trained and wise physician use a Recovery Hospital as an escape from the intolerable family situation. Many others are without funds and have nowhere to go when they leave the institution, which therefore is often forced to act as a hostel for lost and stranded wayfarers. And so

the medical problems for which the patients seek final relief become submerged beneath waves of personal and social relationships and world economics.

Medical men have always realized that when a new remedy like penicillin appears, which "cures" a definite disease in the mass, the intimate relationship between patient and doctor, which Jung calls "le participation mystique," tends to diminish. Moreover, the shortened period of illness, which often results from new drugs, hardly permits more than a "how-do-you-do, good-bye" relationship. In preventive medicine there is not much personal interchange between the Board of Health doctor and his 5,000 vaccinees.

Treatment of the acute phase of disease in a general hospital, where tangible ills are handled in heroic fashion, has much in common with the Greek concept of profane medicine. In sharp contrast, the recovery phase of disease should call forth the special technics which have now been developed to perform the work of sacred medicine. The patient, exhausted by his bout of acute sickness, feels unlike his former self; he is a strange and unaccustomed pilot in his own conning tower. He finds himself doubtfully suspended between what went before and what lies ahead. He reaches for a guiding hand and should find one whose sensitive and powerful grasp provides exactly the correct proportions of direct help and insistence upon the achievement of self-help. In the recovery phase of disease, therefore, the physician should encompass all the skills of sacred and profane medicine with which to restore the patient to his original wholeness; short of that the patient will have learned to accept his residual handicap and find a way to carry on in spite of it.

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Pulmonary Paragonimiasis

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OBSERVATIONS of twelve cases of paragonimiasis among Filipino guerrillas hospitalized in a large general hospital on the island of Leyte are presented because the cases are of unusual interest and also because the disease may be encountered in the future in the United States where it has hitherto been practically non-existent. Miller and Wilbur in 1944 reported three cases, with mention of four others, in returning veterans.⁶

Paragonimiasis, also known by the terms pulmonary distomatosis, pulmonary distomiasis, parasitical hemoptysis, gregarinosis pulmonis, endemic hemoptysis and oriental lung fluke disease, is produced in man by the invasion of the trematode *Paragonimus* through the ingestion of infected raw or incompletely cooked crab or crayfish.

Paragonimiasis is widely distributed. The parasite was originally found in the lungs of a tiger in a zoo in Amsterdam, Holland, in 1877 and was described by Kerbert in 1878 and named *Distoma westermani* in honor of the director. In 1880 Mason in a letter described eggs in the sputum of a Chinese male and referred to a parasite in the lungs found by Ringer in still another patient. This fluke, sent to Cobbold, the recipient of Mason's letter, was named *D. ringeri* by Cobbold. Shortly afterward Baelz in Japan also discovered eggs in sputum and named the parasite *D. pulmonale*. In 1889 Leukart, comparing the worm of Baelz and the worm of Kerbert, found them quite similar except for minor differences. This conclusion has been widely accepted. In 1899 (Braun) the parasite was placed in a new genus, *Paragonimus*, and *P. westermani* was employed, commonly because of priority, synonymously for *P.*

ringeri. This usage is not agreeable to those who favor the existence of several distinct species of the trematode.

Ward in 1894 found a fluke in a cat from Michigan but because of the possibility that the cat had been imported could not call it endemic to North America. Somewhat later that same year Kellicot found a similar fluke in a dog from Ohio and in 1908 Ward named it after Kellicot, *P. kellicoti*. Nakagawa in 1917 described the life cycle of the lung fluke in Japan and in 1934 Ameel worked out in detail the life cycle of the lung fluke in North America.

There has been considerable controversy among workers regarding differentiation of the species of *Paragonimus*. Ameel in 1934, after a careful study which implied the possibility of one species, stated that "in the absence of conclusive evidence either to support or contradict the work of Ward and Hirsch, it is believed advisable to recognize the species considered valid by them, namely, *Paragonimus westermani*, *P. ringeri* and *P. kellicoti*. Likewise *P. compactus*, recognized as a distinct species by Vevers, should be retained until it is restudied."

Paragonimiasis has been found in men and other mammals, including the cat, dog, hog, goat, fox, wolf, leopard, wild cat, panther, wolverine, beaver, mink, mongoose and civet cat. Although hyperendemic foci for man exist in the Far East, Japan, Korea, Formosa and the Philippine Islands, it is found elsewhere. The most recent publication, *Manual of Tropical Medicine* (National Research Council), states that the disease has been found in Africa (Belgian Congo, British Cameroons, French West Africa and Tripoli), Central China, French Indo-China, Manchuria, Samoan Islands,

Malay Peninsula, New Guinea, India (Assam, Bengal, Malabar, Madras and Presidency) and South America (Brazil, Peru, Ecuador and Venezuela). There is uncertainty as to the presence of the disease in the Netherlands Indies.

According to Khaw, the disease has been found in the United States in the cat, dog, hog, wild cat, goat and mink. Ohio, Minnesota, Wisconsin, California, South Carolina, Mississippi, New York and Kentucky have at times produced the infected animals. With the exception of California, where the infected cats and dogs were found in the oriental quarters of San Francisco and could possibly have been imported, it would appear that the remaining states can provide the intermediary hosts necessary for infection. Ameel in a survey found suitable crayfish and snails in Kentucky and Tennessee, none of which were infected, and he points out that although the disease is at present confined to domestic and fur-bearing animals in the Americas it must be looked upon as a potential human parasite.

The parasite, like all trematodes, has a complex life cycle. The egg is either coughed up in the sputum, passed in the feces or, less commonly, escapes by way of the ulcerated skin. It is rather large, oval, operculated, and yellow to dark brown in color. Its dimensions vary but, as generally given, measure 85 to 100 micra in length and 50 to 65 micra in width.

Upon reaching water development proceeds within a few weeks by hatching of miracidia which in turn penetrate snails of several species. Several months elapse for the transformation of miracidia through the stages of sporocysts, rediae and cercariae. Cercariae invade the second intermediate host, a crustacean (either a crab or crayfish of many species), and encyst in the muscles as metacercariae. Following the ingestion of an infected crab or crayfish, these are released in the alimentary tract which is penetrated in the region of the jejunum. After entrance into the peritoneal cavity the diaphragm is invaded, then the

pleural cavities and eventually the lung where the majority of parasites mature.

The mature worm is dark reddish-brown in color and its shape is oval verging on the spherical. It measures 8 to 20 mm. in length and 5 to 9 mm. in width. While not actively motile outside the lung, movement of various portions of the worm can be observed when it is freshly removed from the tissue of the host. A thick skin of cuticle covering the worm is overlain with scale-like spines. There are two suckers, an oval terminal and a ventral just cephalad of the mid-portion of the body. The alimentary tract is rudimentary, consisting of pharynx and esophagus dividing into two intestinal ceca which end blindly at the caudal end. The testes lie on both sides of the midline posterior to the uterus which is centrally located opposite the branched ovary, slightly posterior. The excretory system consists of a large, elongated excretory sinus lying in the mid-axis of the body terminating in an excretory pore on the dorsal surface.

PATHOLOGY

The earliest lesions of paragonimiasis produced experimentally in the lungs of kittens and puppies according to Nakagawa may be seen three days after feeding as pin-head hemorrhagic spots which become dark red in fourteen days. Within twenty-one to twenty-five days pale cysts may be seen at the site of the petechiae. About forty-five days after feeding the cysts are dark red and are surrounded by leukocytes, round cells and erythrocytes. In another week a vacuole is present which may contain a worm but very often the worm has gone into the surrounding tissue. Ninety days after feeding the cysts are bluish-grey, the vacuole has increased in size and porridge-like material containing one or two mature worms may be present. The cyst wall may be intact or in communication with an air space, bronchus or pulmonary vein radical. Eggs may also be noted at this time either in the cyst or parenchyma of the lung where erythro-

cytes, leukocytes, epithelial cells and débris also are gathered. The bronchioles and bronchi may also be dilated, containing red cells, leukocytes and eggs.

Musgrave in 1907 described the autopsy findings in eight cases of paragonimiasis in the human. The lesions in these cases were massive and far advanced. Almost every organ with the exception of the stomach was involved. The diaphragm was involved in every case. The pleura, lungs, omentum, small intestine, large intestine and the surface of the liver beneath the capsule were affected in five or more of the eight cases. The pectoralis major and psoas muscles, the pericardium and heart, spleen, pancreas, appendix, kidney, bladder, scrotum, prostate and brain less frequently also contained typical lesions. He called special attention to the involvement of the superficial, subcutaneous and deep mesenteric nodes which in two cases had broken down in the axillary and in one case in the inguinal regions. Musgrave describes the characteristic lesion as a necrotic abscess, of a peculiar dull bluish-slate color with a definite wall made up of layers whose outer surface is connected with surrounding tissue and whose inner surface is a smooth membrane; an anchovy-like sauce material fills the cavity in which adult worms and eggs may or may not be present. Occasionally the central material may resemble ordinary pus or be caseous. Inflammatory reaction is generally absent surrounding the lesions.

In addition Musgrave described: (1) non-suppurative lesions found as adhesions between pleural surfaces which contained ova; (2) a tubercle lesion generally in the lung; (3) in loose connective tissue, as simple infiltration with ova or as hyperplasia containing ova or, when in the lung, as focal specific pneumonia lesions in which the presence of parasites and ova is variable; (4) a suppurative lesion resembling ordinary pyogenic lesions, frequently containing ova; (5) ulcerative lesions in the skin in association with breakdown of lymph nodes and also in the mucous membrane of the bronchi and the intestine. Such pathologic

involvement can produce different clinical syndromes. As the cases indicate various pulmonary lesions may be encountered.

Clinical Findings. Clinically, the patient presents the picture of a slowly progressive pulmonary disease. Musgrave speaks of an acute form of the disease in which the course is rapidly downhill. It should be recalled that he was primarily interested in the pathology of the disease and that his cases occurred in prisoners over forty years ago. At that time and amidst such surroundings clinical histories were either meager or lacking. In addition, complicating conditions common to prisoners in that location, such as severe malnutrition, beri-beri and amebic dysentery, were coexistent.

The onset of symptoms in our patients varied from one week to thirty-four months prior to observation so that both early and late cases were seen. In all but one instance a definite history of fresh-water shellfish ingestion was obtained, but due to the frequent inclusion of shellfish in the diet it was not possible to determine the time relation of the onset of the first symptom to this exposure. The illness began insidiously in five patients following a febrile episode clinically diagnosed malaria but not confirmed by laboratory study. The incidence of malaria is so high in these regions that the patients' description of their illness and its response to antimalarial therapy prompt us to accept the diagnosis of malaria as probably correct. The introduction of the disease in these five patients was so similar that one wonders whether malaria specifically or as an acute debilitating febrile disease precipitated the appearance of the clinical symptoms of paragonimiasis. Three patients stated that they were feverish and chilly at the onset but that the fever cleared in a few days and a cough continued. In over one-half the patients, therefore, the onset was associated directly or indirectly with fever.

In all patients cough or hemoptysis, gradually increasing in severity, was the first symptom of the disease. The cough, at first dry and irritating, rapidly became

productive of sputum. The cough was present throughout the day and was increased by effort and fatigue. It was more marked in the early evening and early morning and in three patients it was especially prominent at night. The sputum characteristically contained flecks of dark blood. While hemoptysis was present in all patients, its onset varied; in some it appeared early, in others late and in two patients it did not appear until two years following the onset of the cough (Cases III and XI). Although more often tenacious, thin watery sputum was seen and the color varied from a yellow-white to frankly bloody. Dark greenish sputum was encountered only in those patients who had associated tuberculosis. The sputum from which ova were most frequently recovered was gelatinous, purulent, bloody and of a slightly sour odor in which were scattered dark brownish-red flecks resembling cigarette tobacco shreds. The amount of sputum produced daily ranged from 30 to 90 cc. and varied at times in the same patient.

Chest pain was present in all but one patient (Case II) during the course of illness. Pain was related to respiratory motion in only five patients, in the others it was described as deep in the chest, sticking, transient and shifting or increased by cough and activity. Rarely it could not be definitely localized.

Two-thirds of the patients complained of loss of weight, weakness and tiredness. These symptoms were difficult to evaluate as all patients carried out arduous duties at the onset of the disease and for some time thereafter, and their appearance in the majority of instances did not suggest weight loss. In only two histories (Cases I and x) could it be stated with reasonable accuracy that weight losses of 20 and 26 pounds had occurred. Dyspnea occurred in five patients, three of who had accompanying effusion; in the remaining two the parenchymal lesion was apparently responsible. Four patients complained of night sweats and in only one of these was fever detected during hospitalization. Gastrointestinal symptoms

such as anorexia and vomiting were encountered occasionally. In two patients a history of hematemesis was present. Although we questioned both patients in great detail we could not be certain whether pulmonary or gastrointestinal bleeding had occurred; hepatomegaly and splenomegaly were not present in either case.

Two patients (Cases VIII and x) complained of pain in the extremities. We were not familiar with Musgrave's findings at that time indicating involvement by the fluke of muscle and lymph nodes. Physical examination offered no adequate explanation for these symptoms, which gradually disappeared. Palpitation occurred in two patients with pleural effusion, in neither of whom were we able to demonstrate by physical examination, x-ray or electrocardiographic study any striking abnormality of the heart. (Table I.)

Physical Findings. The relative well being of these patients, with few exceptions, was noted by almost every observer. In spite of the history of prolonged cough and hemoptysis the majority of patients did not appear to be sick. The few who appeared ill on the first examination invariably were those patients who had fluid in their pleural cavity, but not all patients with empyema appeared sick in the sense associated with pyogenic empyema. Loss of weight, although prominent in the history, was frequently not apparent upon physical examination.

The temperature during hospitalization exceeded 102°F. in two cases (Cases IX and XI), ranging between 99 to 100°F. for more than seven days in Cases I and VI and was either normal or reached 100.2°F. for one to three days in the remainder throughout the months of hospitalization. Prolonged fever was associated with the presence of pleural fluid but fever was not present in all patients who had fluid.

Physical signs indicative of pulmonary disease were present in all of the patients at some time in their hospitalization prior to therapy. These findings were not constant and were at variance with those reported

by Bercovitz. A possible explanation for this difference may be that these patients were hospitalized and were examined more frequently over a course of many months. Râles were present in eleven of the twelve patients. These varied from fine to coarse

identified when seen, staining will mask their presence. In Case XI, for example, twenty-four specimens were searched for tubercle bacilli before a drop of sputum was directly examined and ova of *P. westermani* were found in the second examination. Ova

TABLE 1
SYMPTOMS IN REPORTED CASES

Case No. . . .	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Duration . . .	24 mo.	6 mo.	24 mo.	1 wk.	8 mo.	16 mo.	8 mo.	3 mo.	12 mo.	18 mo.	33 mo.	34 mo.
Onset	Malaria; pain; hemoptyses	Cough	Malaria; cough	Acute fever; hemoptyses	Anorexia; cough; weakness	Fever; chills; hemoptyses	Cough; hemoptyses	Fever; cough; hemoptyses	Cough	Malaria; hemoptyses	Cough	Malaria; cough; chest pain
Cough	+	+	Nocturnal	+	+	Nocturnal	+	Nocturnal	+	+	+	+
Hemoptyses . .	+	+	+	+	+	+	+	+	+	+	+	+
Chest pain . .	Not resp.	0	Resp.	Not resp.	Resp.	Resp.	Not resp.	Not resp.	Resp.	Not resp.	With cough	Resp.
Loss weight . .	+	0	±	0	+	+	±	0	0	+	+	+
Weakness . . .	+	0	+	0	+	+	0	0	0	+	+	+
Fatigue	+	0	+	0	+	+	0	0	0	+	+	+
Dyspnea	0	0	+	0	+	0	0	0	0	+	+	+
Vomiting	0	0	+	0	0	0	blood	0	0	0	Blood	+
Palpitation . .	0	0	+	0	0	0	0	0	0	+	0	0
Pain in extremities	0	0	0	0	0	0	0	+	0	+	0	0
Anorexia	0	0	0	0	+	0	0	0	0	0	0	+
Night sweats .	0	0	0	0	0	0	+	0	0	+	?	+

in character and were heard in varying portions of the lungs. Musical, sibilant and sonorous râles were rarely heard. Characteristic signs of fluid were present in only two of these patients (Cases III and X).

There were no noteworthy findings referable to the heart; a very large, smooth, non-tender liver was palpable in three patients (Cases II, III and IV); firm, large spleens were present in two patients (Cases II and IV); no unusual adenopathy was encountered.

Laboratory Findings. The laboratory diagnosis of this disease depends upon the recognition of characteristic ova. Ova can be recovered from the sputum, feces, fluid of serous cavities and broken down infected lymph nodes. In our patients ova were found in sputum, feces and pleural fluid.

The type of sputum from which ova are most frequently recovered has been described previously; the presence of scattered brownish-red flecks, closely resembling cigarette tobacco shreds in sputum is re-emphasized as especially indicative of accompanying ova. Although ova are easily

are not produced in the sputum regularly and in quantity so that examination of many specimens is required before it can be assumed that they are absent. Bercovitz mentions a case in which ten examinations were necessary before ova were recovered. We have had similar experiences. When few ova are excreted, concentration techniques are most helpful. In suspicious cases when direct examination of the sputum is fruitless, five or more examinations by concentration technics should be done before concluding that the disease is not present.

Recovery of ova from the stool is more difficult. In seventy-one stool examinations in the twelve patients with positive sputum ova were recovered seven times (Cases I, II, V and VIII).

The pleural fluid in four patients varied from a thin, blood-tinged, serous fluid to a thick, creamy, purulent fluid. Yellowish curd-like particles were present throughout the fluid. Red cells only were identified in the blood-tinged fluid. A paraffin block of the purulent fluid revealed leukocytes in

various stages of degeneration, among which eosinophils were absent. All fluids were negative for organisms upon both smear and culture. Fourteen examinations were made in four patients (Cases III, V, IX and X) and in only one instance (Case X) were ova recovered on five occasions.

The changes noted in the blood counts in this series must be cautiously interpreted as the direct result of paragonimiasis since all patients had, in addition, at least one or more intestinal parasite and many had either observed malaria or had a history of recurrent malaria.

The average hemoglobin (Sahli) prior to therapy was 83 per cent, the average erythrocyte count was 4,300,000 per cu.mm. and the average leukocyte count was 11,300 per cu.mm. These findings check closely with Bercovitz's report of 78 per cent average hemoglobin and 4,303,000 per cu.mm. erythrocyte count in twenty patients. The hemoglobin ranged from 70 to 100 per cent and the red cell count from 3,100,000 to 5,400,000. Leukocytosis ranging from 15,000 to 21,000 was seen in every case in which fluid was present and was encountered twice in the absence of fluid. It seems probable that initial leukocytosis does not occur in the absence of complication, as values from 6 to 10,000 leukocytes were seen in patients whose duration of symptoms varied from one week to one year. Eosinophilia was present in all patients. We believe this finding was due to accompanying parasites commonly responsible for high eosinophilic values. Most authors state that paragonimiasis is not accompanied by eosinophilia. (Table II.)

Following the use of emetine and anthelmintics, there was a slight increase in the hemoglobin and red cell count and a decrease in the leukocyte count.

The erythrocyte sedimentation rate was elevated above 20 mm. per hour in ten patients. The highest level reached was 68 mm. per hour in a patient with hydrothorax and coexistent tuberculosis. The rate was always elevated in the presence of fluid. In five patients (Cases II, IV, V, VI

and VII) it became normal prior to the administration of emetine therapy. In one case aspiration of fluid may have produced this result. In four patients (Cases I, V, XI and XII) elevation of the sedimentation rate occurred after treatment; in two such instances (Cases V and XII) tuberculosis was coexistent. In two patients (Cases III and VIII) the sedimentation rate decreased but was still elevated following treatment and in only one instance (Case X) was it normal both after removal of fluid and emetine administration.

Our data do not permit thorough evaluation of the sedimentation rate in this disease; the results were too widely scattered and the cases too few. It can be pointed out, however, that a normal sedimentation rate does not preclude the presence of ova in the sputum.

Transiently positive serologic tests were noted in four patients (Cases I, II, V and IX) both by the Kahn test and Wassermann reaction. The four patients concerned denied initial lesions and had no external manifestations of either syphilis or yaws. These equivocal reactions involving one-third of the patients stimulated serum protein studies. Seven patients (Cases I, II, III, V, VIII, IX and XI) showed an increase in serum globulin. Above 3.0 Gm. per cent most showed some fall in albumin, the total serum protein levels remaining within normal limits. (Table III.) Serum protein changes have been reported in many diseases, including tuberculosis, malaria and schistosomiasis. These diseases were present in four of the patients (Cases I, III, V and VII). Hepatic disease may have contributed to the serum protein changes in two instances. (Cases II and III.) In Cases VIII, IX and XI the serum protein variation could not be explained except as a result of paragonimiasis.

The urinary findings were normal in all patients.

Roentgenologic Observations. Eleven patients showed involvement of the lung in the initial x-ray of the chest. The twelfth subject (Case VIII) showed extremely heavy

TABLE II
HEMATOLOGIC FINDINGS

Casc	Date	Hgb.	R.B.C. (mil- lion)	W.B.C.	Polys.	Lymphs.	Eosino- philes	E.S.R.	Other Parasites	Comments
I	8/30/45	36	A. lumbricoides	
	9/11/45	8,800	54	14	32	..	Hookworm	
	9/24/45	90	4.65	8,000	52	27	21	29	T. trichiura	
	10/ 6/45	14,400	53	13	34	48	S. japonica	
	11/ 7/45	15		
	11/16/45	80	4.2	9,600	62	38	14			
II	3/20/45	75	4.8	9,000	A. lumbricoides	
	5/17/45	85	4.2	8,000	62	38	..	13	Hookworm	
	9/ 1/45	6,200	46	42	12	..	E. histolytica	
	9/19/45	95	4.7	6,400	45	46	9	12	T. trichiura	
	9/24/45	7,200	48	41	11	4		
	10/21/45	8,400	64	24	12	14		
III	9/12/45	14,600	49	17	34	..	A. lumbricoides	Fluid; tuber- culosis
	10/ 4/45	16,800	51	18	31	68	Hookworm	
	10/25/45	85	4.4	14,800	25	19	56	26	T. trichiura	
	11/15/45	100	5.2	10,400	51	22	47	23		
IV	9/14/45	5,200	48	48	4	14	A. lumbricoides	Tuberculosis
	9/21/45	95	5,800	59	38	3	15	Hookworm	
	9/25/45	5,600	46	46	8	6	T. trichiura	
	10/20/45	75	3.7	16		
	11/16/45	85	4.2	6,200	53	44	3	6		
V	2/27/45	21,900	72	19	9	..	E. nana	Fluid; tuber- culosis
	8/30/45	44	T. trichiura	
	9/19/45	95	4.8	15,800	36	22	42	16	Hookworm	
	11/ 7/45	9,400	41	38	21			
	11/17/45	5,900	52	30	18	33		
VI	6/26/45	9,600	43	46	11	36	A. lumbricoides	
	8/14/45	70	4.3	17,500	58	22	20	8	Hookworm	
	9/22/45	13	T. trichiura	
	10/19/45	95	4.9	10,400	51	30	19	11		
	11/16/45	90	4.6	9,600						
VII	6/ 2/45	80	4.2	9,400	46	24	30	39	A. lumbricoides	
	7/10/45	7,900	52	25	23	..	Hookworm	
	9/ 4/45	9,800	22	40	38	1	T. trichiura	
	10/12/45	4		
	10/31/45	80	4.2	9,200	32	42	26	8		
VIII	10/ 8/45	80	3.9	8,700	49	32	19	54	Hookworm	
	10/25/45	75	3.8	10,400	40	20	40			
	11/13/45	60	3.4	8,800	44	30	26	46		
IX	9/17/45	80	4.0	15,200	56	28	16	..	A. lumbricoides	Fluid
	10/24/45	10,800	43	39	18	..	Hookworm	
	11/ 6/45	36	T. trichiura	
	11/15/45	90	4.7	9,900	28	51	21			
X	6/ 9/45	15,900	44	30	26	48	A. lumbricoides	Fluid
	6/15/45	100	5.4	21,000	64	21	15	..	S. stercoralis	
	6/30/45	18,800	67	14	9	..	Hookworm	
	7/13/45	78	17,300	61	33	6			
	7/24/45	80	4.4	15,400	65	19	16			
	8/ 7/45	85	4.7	6,700	75	17	8	48		
	9/11/45	8,400	54	28	18	48		
	10/16/45	100	5.5	8,000	54	34	12	11		
	11/15/45	7		
XI	7/16/45	80	4.1	12,800	70	30	..	8	Hookworm	
	11/ 1/45	95	5.0	10,500	50	37	13	30	T. trichiura	
XII	9/10/45	70	3.4	15,400	48	20	32	32	Hookworm	Tuberculosis
	10/20/45	75	4.0	14,200	55	27	18	55	E. nana A. lumbricoides	

peribronchial markings in the initial film and ten days later an area of parenchymal infiltration was noted.

The changes seen could be divided roughly into two groups: in one group the

lung and the upper lobe. Both lungs were involved in five subjects (Cases I, II, VI, XI and XII). One lobe invasion was seen in only four instances (Cases IV, VII, VIII and IX).

The massive lesions in which the x-ray

TABLE III

SERUM PROTEINS, NON-PROTEIN NITROGEN, FORMOL GEL TEST, DISTILLED WATER TEST, KAHN AND WASSERMANN TESTS IN TWELVE CASES OF PARAGONIMIASIS

Case	Date	Total Protein Gm. %	Albumin Gm. %	Globulin Gm. %	Albumin Globulin Ratio	N.P.N. mg. %	Formol Gel Test	Distilled Water Test	Kahn Test	Wasser- mann Test
I	9/11/45	7.8	+	+	?	++
	9/19/45	7.4	3.2	4.2	0.8	?	-
	11/16/45	5.8	3.4	2.4	1.6	32	-	
II	9/11/45	7.7								
	9/19/45	7.0	3.6	3.4	1.1	?	-
	10/26/45	6.5	3.7	2.8	1.3	29	-	+	-	
	11/16/45	6.0	3.6	2.4	1.5					
III	10/24/45	7.4	3.0	4.4	.68	..	+	+++	-	
	10/25/45	7.5	3.1	4.4	1.7	42	-	
IV	9/21/45	6.3	3.5	2.8	1/3	..	-	++	-	
	9/25/45	5.8	3.4	2.4	1.6					
	10/15/45	6.1	4.0	2.1	1.9					
	11/16/45	6.4	4.2	2.2	1.8					
V	9/13/45	7.5	3.4	4.1	.8	-	
	9/19/45	7.0	2.8	4.2	.7	+	-
	11/17/45	5.7	4.1	1.6	2.5	24	-	+	-	
VI	10/19/45	6.5	5.1	1.4	3.6					
	11/17/45	6.5	3.9	2.5	1.6	..	-	-	-	
VII	10/31/45	5.7	3.6	2.1	1.7	..	-	-	-	
VIII	10/12/45	6.9	3.0	3.9	.75	..	-	++	-	
IX	11/7/45	6.7	3.8	2.9	1.2	..	-	++	?	±
	11/12/45	6.9	3.5	3.4	1.0	..	-	-	?	-
X	10/16/45	6.1	5.0	1.1	4.5	35	-	-	-	
XI	10/30/45	7.4	3.9	3.5	1.1	..	-	++	-	
	11/16/45	6.2	3.6	2.6	1.7	-	
XII	10/20/45	6.1	4.6	1.5	3.1	35	-	-	-	-

involvement was massive and large areas of density were present (Cases III, IV, V, VII, IX and X); in the second group the changes were diffuse and the lesions were small, soft and generally multiple (Cases I, II, VI, XI and XII). The right lung and the lower lobe were more frequently affected than the left

shadow indicated consolidation, abscess cavity or fluid had no discernible specific characteristics which suggested the presence of paragonimiasis. Frequently small areas of infiltration were present in the upper lobes in these cases resulting in the diagnosis of tuberculosis. In Case III these shadows

preceded the onset of fluid and were associated with the presence of both tubercle bacilli and typical ova; in Case v the shadows followed the appearance of fluid and were also associated with both tubercle bacilli and ova. Within two months after therapy these small areas of involvement were markedly diminished in size in Case iii and had entirely disappeared in Case v. A small area of infiltration was seen in two other patients (Cases ix and x) complicated by fluid. In neither case were tubercle bacilli found and in Case x typical ova were repeatedly recovered from the pleural fluid.

The etiology of the x-ray shadows in these cases must remain moot in the absence of pathologic examination and prolonged follow-up. The resolution of the lesions in such short periods under observation, if tuberculous, seemed most unusual. Tubercle bacilli were found only rarely in spite of assiduous search, and the disappearance of ova and decrease of sputum roughly paralleled the clinical and x-ray improvement. The presence of tuberculosis is undeniable in these cases but whether this disease was responsible solely for the x-ray appearance may be questioned. It is more likely that the association of tuberculosis and paragonimiasis contributed to the roentgenologic picture, but the subjective relief and decrease of pulmonary symptoms following emetine suggest that the rôle of the fluke was more important than that of the tubercle bacilli in causing the x-ray changes.

In one patient a large abscess cavity was noted in the right lower lobe. This closed spontaneously, prior to therapy, over a period of five months. Following therapy, this shadow had cleared only slightly in one month.

The lesions (Cases I, II, VI, XI and XII) which are believed strongly suggestive of paragonimiasis may be simulated by the early pulmonary lesions of *S. japonica*. The pattern seen follows the experimental mode of spread in that the lower lobes of both lungs are involved primarily by small soft

areas measuring 1 to 2 cm. in diameter. Larger lesions are encountered close to the diaphragm. In the upper lobes the first and second interspace are rarely involved. At times the shadows assume a patchy distribution in the lateral lung fields. While the general impression is one of mottling, the lesions are larger, less numerous, more discrete and not as dense as those seen in miliary tuberculosis. (Figs. 1 and 2.)

Therapy resulted in the disappearance of the shadows in only case (Case VI). (Figs. 3 and 4.) There was no apparent effect in Cases I, II, XI and XII.

TREATMENT

As the patients were observed for very few months the end results of the treatment are not shown and only the early and immediate effects are available. Tartar emetic (1 per cent) was arbitrarily chosen in the first four cases because it was a drug under constant use in the treatment of schistosomiasis. It was employed in Cases I, II, IV and V and it was badly tolerated. Cough, sputum and chest pain were markedly increased immediately and for some time after injection. There was no diminution, moreover, in the excretion of ova. Emetine hydrochloride intramuscularly was substituted and continued thereafter in all patients. This drug was well tolerated, reactions were few and when present were minor in nature.

The effect of treatment was assessed by the evaluation of relief of symptoms, the disappearance of ova in the sputum and the resolution of the x-ray shadows.

Symptomatic Relief. Nine of the twelve patients received definite subjective relief in a short period of time. This period followed shortly after the injections of a total dosage of 0.3 to 0.36 Gm. of emetine hydrochloride. Pulmonary symptoms such as chest pain, cough and sputum decreased. Although a sense of well being appeared relatively quickly, there was a lag between the decrease in frequency and severity of the cough and the decrease of sputum.



FIG. 1. Characteristic lesions of pulmonary paragonimiasis (Case II, August 26, 1945).



FIG. 2. Pyopneumothorax and empyema illustrating massive lesions in paragonimiasis (Case X, October 14, 1945).

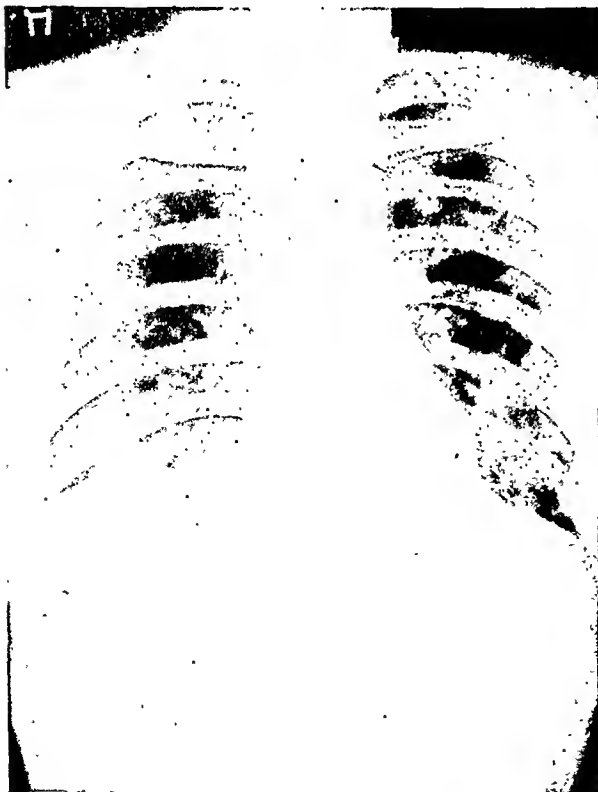


FIG. 3. Film demonstrates increased basal involvement and characteristic mottling prior to therapy (Case VI, August 28, 1945).

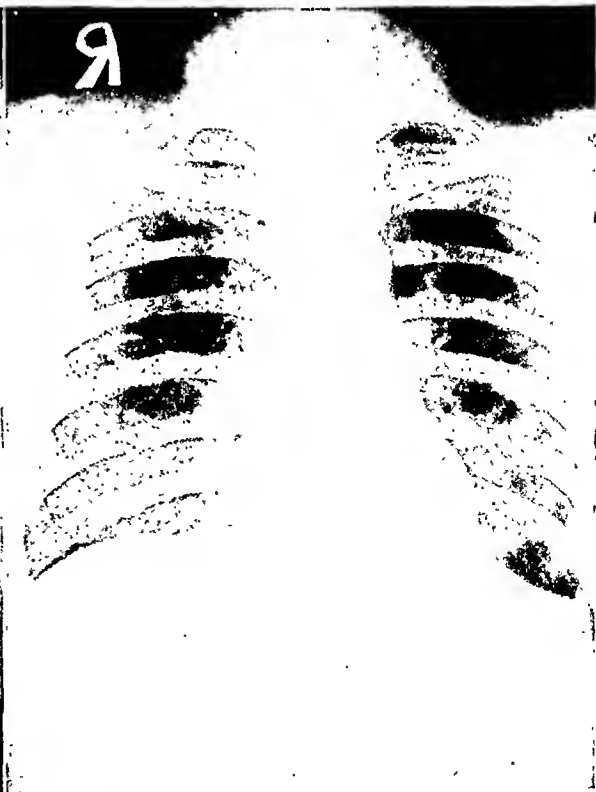


FIG. 4. Film from the same patient showing disappearance of lesions three months later (Case VI, November 15, 1945).

Disappearance of Ova. Experience in the detection of ova in sputum in this disease produces caution in the evaluation of results based upon the disappearance of ova. Negative examination for many days interposed between the demonstration of ova are not uncommon. In these cases ova were discovered in seven of twelve patients, one and thirty days following the first course of treatment. Although in this compilation of cases emetine employed for any indication was considered a course and hence varied in amounts from 0.1 to 0.54 Gm., it would appear significant that ova were found after a dosage of 0.54 Gm. of the drug.

There was no apparent relationship between the duration of symptoms and the effect of emetine on the disappearance of ova as the following table indicates:

<i>Duration of Symptoms (Months)</i>	<i>Sputum Positive (Case)</i>	<i>Sputum Negative after Therapy (Case)</i>
1-6	viii	
7-12	ii, vii, ix	v
13-18	x	
19-24		vi
25-30	xiii	
31-36	i, xi	xii

All cases are included above as positive in which ova were found after treatment even though in three instances Cases vi (0.48 Gm.), viii (0.54 Gm.) and xi (0.48 Gm.) the sputum became negative the second day after treatment and apparently remained so thereafter. Following the second course of therapy, the sputum became negative in three cases. In Case x in which the sputum was repeatedly negative three courses were necessary to secure a negative pleural fluid.

The cases in this series are too few to permit determination of the optimum amount of drug required for the disappearance of ova. Ova were found on at least the first day after 0.54 Gm. had been administered and pleural fluid still produced ova after 1.2 Gm. of the drug. In eleven of

twelve cases sputum and pleural fluid were negative at the conclusion of the observation period. The one remaining positive case (Case vii) had had only one course of 0.48 Gm. of emetine. In four patients (Cases i, ii, ix and x) disappearance of ova persisting after one course was accomplished by repetition of emetine.

X-ray. The shadows demonstrated by x-ray regressed in less than one-half the patients after emetine administration. In only three instances (Cases v, vi and x) was a relatively normal chest film obtained, and in two subjects (Cases iii and ix) there were signs of slight to moderate resolution. In the remaining patients there was no evidence of change. Four of the five patients in whom x-ray improvement took place were those in whom fluid had been demonstrated. Only one subject (Case vi) showed resolution of parenchymal involvement. The possibility remains that if a follow-up had been available, the x-ray results might have been better as in only one case was a film taken as long as five months after the first course of emetine. In the remainder the time interval was less than two months.

In summary, tartar emetic was tolerated poorly by four patients and did not appear effective in its brief trial. Emetine hydrochloride resulted in prompt and considerable subjective relief. Its repeated use was followed by the disappearance of ova in the sputum and pleural fluid in one instance. There was only slight effect on the pulmonary parenchymal change within two months following its administration.

DIAGNOSIS

When the pathology of paragonimiasis is recalled, it is apparent that many pulmonary diseases may be simulated. The non-specific symptoms and physical findings of paragonimiasis require that diagnosis be dependent upon recovery of ova. There are, however, features of the disease which aid in its diagnosis and lead to a more intensive search for ova.

The history may indicate exposure in an endemic region or may even disclose the

ingestion of raw, wine-soaked or incompletely cooked fresh-water crabs or crayfish. The minimal systemic reaction, lack of fever, weight loss, sweats and asthenia, is striking on physical examination. The relative well being of the patient seems incongruous when it is contrasted with the type and duration of the symptoms. Although all our patients presented some physical findings in the lungs, these were minimal when consideration was given to the pathologic involvement noted by x-ray and the presence of hemoptysis of long duration. Others have cited the paucity of physical signs in this disease. X-ray of the chest is most helpful in diagnosis. Bizarre multiple lesions such as have been described should focus attention upon the possibility of a parasitic infection, and normal lung x-rays in the presence of hemoptysis and a history of sojourn in an endemic region should direct attention to the possibility of paragonimiasis. Suspicion of the disease is the important thing and a search of unstained sputum for ova should be made in every instance in which exposure is established and protracted cough exists.

CASE REPORTS

CASE I. A twenty-nine year old Filipino male was admitted August 27, 1945, complaining of cough, intermittent hemoptysis and pain in the chest of two years' duration.

Following a recurrence of malaria in February, 1943, he noted pain in the right chest and hemoptysis. During the next two and one-half years he lost 20 pounds, became weak and tired and developed a constant cough productive of blood-streaked sputum. He had always eaten raw shrimp, crab and crayfish, and continued this practice in the mountainous regions of Mindanao as a guerrilla. Other than malaria in 1942 he denied all illnesses. There was no family history of pulmonary tuberculosis.

On admission to a hospital on June 22, 1945, bilateral apical râles were noted. X-ray examination showed several areas of soft and fibrous infiltration in the right upper and middle lung fields with suggestion of cavitation in several areas. Sputum was negative for tubercle bacilli. There was no fever during the remainder of his

two-month stay and he was eventually transferred to this hospital.

Physical examination revealed a Filipino male not acutely ill; temperature 98.6°F.; pulse 68; respirations 18, weight 120 pounds; blood pressure 100/80. There were numerous crepitant râles at the right apex and the inner mid-scapula region. A leukocyte count was 8,800 per cu.mm. with 54 per cent neutrophils, 14 per cent lymphocytes and 32 per cent eosinophils. The sedimentation rate was 36 mm. in one hour. A smear for malarial parasites was negative. The sputum was negative on four occasions for tubercle bacilli but contained ova of *P. westermani* repeatedly. The stool contained ova of *A. lumbricoides*, hookworm and *P. westermani*. Urinalysis was negative. The Kahn test was doubtful, and the Wassermann was two plus on September 11th and negative on September 25th.

Treatment with tartar emetic (2 per cent solution) was started on September 10th and was discontinued September 27th after 39 cc. had been given because of severe reaction and apparent lack of beneficial effect. Emetine hydrochloride (0.06 Gm. daily) was begun September 29th and continued for six days.

About one week following the combined treatment it was noted that 10 pounds loss of weight had occurred, chest pain had cleared, cough was less and afternoon fever had appeared, ranging between 99° and 100°F. This continued for three weeks until October 31st. Occasional blood-streaked, mucopurulent sputum still contained ova two weeks following emetine. In the next week the weight increased 2 pounds and the cough and sputum had strikingly decreased to less than 12 cc. daily. There was no roentgenologic change. Schistosomiasis was detected proctoscopically about this time but it was determined to re-treat the paragonimiasis. On October 31st another course of emetine (0.06 Gm. daily) was begun and continued for eight days. About one week later although there was a weight gain of 4 pounds, the cough and chest pain were still present occasionally. The following week there was further subjective improvement, the symptoms were minimal and the sputum had decreased to such degree that it was difficult to obtain a specimen for examination. An x-ray of the lung on November 16th showed no change.

CASE II. A twenty-five year old Filipino male was transferred to this hospital on Au-

gust 26, 1945, with a diagnosis of pulmonary paragonimiasis.

The history of his present illness dated back to February, 1945, when he developed a cough productive of brownish-colored sputum containing specks of blood the size of rice grains. He was hospitalized March 2, 1945, because of hemoptysis. He had been in good health and denied all illnesses except intestinal parasite infestation as a child. Born in Leyte, P.I. he was very fond of raw crayfish, crabs and shrimps which had frequently been his only source of food as a guerrilla. There was no family history of tuberculosis. During hospitalization he had been afebrile; examination had shown medium râles at the left base and fine crepitant râles at the right apex. An x-ray of the chest on March 20, 1945, showed hard and soft irregular mottled densities through both lung fields. Several areas were considered suggestive of cavitation. No change was noted by x-ray on four occasions in the next six months and cavitation was not substantiated. The sputum contained ova of *P. westermani* on April 9th; tubercle bacilli were not found on three examinations. The hemoglobin was 75 per cent, erythrocytes 4,800,000 per cu. mm., leukocytes 8,000 per cu. mm. with 62 per cent neutrophils and 38 per cent lymphocytes. Urinalysis was negative. Ova of *A. lumbricoides* were present in the stool. No specific treatment was given other than hexylresorcinol for the ascariasis.

On admission he weighed 138 pounds and did not appear ill. His general appearance was in striking contrast with the findings in the x-rays of his chest. There were medium râles at the axilla and the left base. There was a short apical systolic blow which was transmitted; blood pressure 115/60; the spleen was firm and easily felt one finger's breadth below the costal margin.

A smear for malarial parasites was negative. A sedimentation rate was 20 mm. per hour. A Kahn test gave a doubtful and a Wassermann test a negative result. Stools contained ova of hookworm, *A. lumbricoides*, *P. westermani* and cysts of *E. histolytica*. Sputum contained ova of *P. westermani* on September 7th to 14th.

Tartar emetic therapy (2 per cent) was begun on September 14th. His cough continued, intensified in the early morning hours, productive daily of 30 to 60 cc. of tenacious, brownish-streaked sputum containing shreds of blood resembling tobacco flakes. After eight doses of

tartar emetic solution had been given it was discontinued on September 28th. Throughout its administration sporadic sputum examination showed the presence of ova. Following tartar emetic on September 29th, emetine hydrochloride (0.06 Gm.) was given daily for six days. Unfortunately the sputum was not examined during this time. However, it was quite definitely established that ova were still being produced several days after the conclusion of treatment. Subjectively there was striking improvement within one week. On October 10th there were no complaints, cough was infrequent, occasionally productive of mucoid material. His weight was 135 pounds, examination disclosed diminished breath sounds and occasional moist râles at the left base. The liver was palpable three fingers' breadth below the costal margin. Ten days later an unexplained fever reaching 102°F. was present for two days. Sputum not exceeding 8 cc. daily was found to contain ova. The following week the sputum increased to 16 cc. daily although he remained afebrile, and another course of emetine (0.06 Gm.) was started October 31st and completed November 8th. At this time he was asymptomatic except for an occasional cough productive of 4 to 8 cc. of sputum daily. X-rays of the chest October 22nd and November 16th showed no change in the appearance of the mottled infiltration extending throughout both lung fields. The sputum was negative for tubercle bacilli on eleven occasions.

Case III. A twenty-eight year old Filipino male was admitted to another hospital on September 11, 1945, where a detailed history was not obtained. Apparently the only finding of note on admission was a yellow patch on the right tonsil. One week later he had chills, cough, profuse sweats and signs of consolidation in the right lower lobe; his temperature ranged from 99.4° to 103°F. An x-ray at this time revealed irregularly dense infiltration in the left lung. Sputum on five occasions was negative for tubercle bacilli. The leukocyte count was 14,600 per cu. mm. with 49 per cent neutrophils, 16 per cent lymphocytes and 34 per cent eosinophils. The stool contained ova of *A. lumbricoides* and hookworm. A stool culture was negative for pathogens. Urinalysis was negative. Penicillin (20,000 units every three hours) was given for nine days without noticeable effect.

He was admitted on September 25, 1945.

His illness was found to date back to August, 1943, when he developed chills diagnosed clinically as malaria. Recovery was slow and asthenia was especially prominent. An intermittent cough began one month later together with dyspnea on exertion and pain in the left chest increased by respiratory motion. Palpitation, gastric distress, frequent vomiting and weight loss followed. He was admitted to a guerrilla hospital where he stayed for ten months. His cough became especially severe at night but was present only occasionally during the day. Sputum averaged about one cupful daily. He was unable to carry out his duties following hospitalization and remained in his quarters in the mountains until his admission to a U. S. Army hospital in September, 1945. He had been a guerrilla in Cebu, P.I. since the Japanese occupation. He liked seafood and as a guerrilla had frequently existed on raw and semi-cooked crabs and crayfish. He denied all previous illnesses except two attacks of malaria, neither verified by smear. One uncle, a close contact, had tuberculosis but the remainder of the family was in good health. His usual weight was 121 pounds.

On physical examination he no longer appeared acutely ill, his weight was 143 pounds, temperature 98.6°F.; blood pressure 92/60. There was a friction rub with signs of moderate pleural effusion at the left base; the liver was palpable three fingers below the costal margin; the spleen was not felt. A leukocyte count was 16,800 per cu. mm. with 51 per cent neutrophils, 18 per cent lymphocytes and 31 per cent eosinophils. Two smears were negative for malarial parasites. Sputum was negative for tubercle bacilli and ova. On October 6th although the sputum was still negative for tubercle bacilli, it contained ova of *P. westermani*. These were demonstrated repeatedly thereafter. X-ray of the chest on October 5th showed a homogeneous density at the left base which extended up the lateral portion of the chest to the second anterior rib; there was a mottled infiltration in the right apex and in the lower portion of the right upper lobe. Thoracentesis on October 13th yielded 50 cc. of blood-tinged fluid from the left chest; this was negative for organisms on smear and culture and did not contain ova. His condition remained stationary. There was no fever. The sputum, a thin but tenacious fluid occasionally containing dark bloody flecks, measured 60 to 80 cc. daily.

Emetine hydrochloride (0.04 Gm.) was given daily from October 18th to October 29th without reaction. During therapy the sputum on three occasions did not contain ova but the day following the conclusion of therapy, October 30th, ova were present. Tubercle bacilli were found on two occasions, October 29th and November 10th.

Following emetine there was subjective improvement. He stated that he was stronger and the cough, although still present, was definitely less severe and was not increased nocturnally. The sputum had decreased gradually and no longer contained bloody flecks, but was still purulent and excessive in amount three weeks later. He had gained 3 pounds. The physical signs of either fluid or markedly thickened pleura were still present at the left base. X-ray of the chest at this time, November 20th, showed marked pleural thickening at both bases, the left more extensive; in addition there was hazy, streaked infiltration in the medial portion of both bases. The patchy infiltration involving the right upper lobe had resolved considerably.

CASE IV. A thirty year old Filipino male was hospitalized at another institution August 30, 1945, complaining of fever, chest pain and cough of one week's duration. Except for one attack of malaria some years before, he had been well until one week before admission when he felt "feverish" for two days. He then noted a frequent cough productive of a yellow, thin mucopurulent sputum containing rice-sized specks of blood, with the simultaneous appearance of sharp, transient chest pain unaffected by respiration.

He was born on Negros, P.I. and had been a guerrilla there living in the mountains. He was fond of fish and shellfish, both cooked and raw. His usual weight was 115 pounds. There was no family history of tuberculosis.

Physical examination disclosed moist râles at the left base and a palpable spleen edge. An x-ray of the chest showed a soft, mottled infiltration in the left first anterior interspace. He was transferred to this hospital the next day.

On admission the findings were confirmed. He was afebrile. A leukocyte count was 5,200 per cu. mm. with 48 per cent neutrophils, 48 per cent lymphocytes and 4 per cent eosinophils. A sedimentation rate was 14 mm. per one hour. Stools contained ova of *A. lumbricoides*, hookworm and *T. trichiura*. Sputum on September 13th was found to contain one ovum of *P.*

westermani. Repeated daily sputum was negative thereafter until eight days later on September 21st. A tuberculin test (P.P.D.) was negative with the first dilution and weakly positive with the second. Sputum was negative for tubercle bacilli on three examinations.

There was no change in the general condition in the next three weeks; frequent cough with bloody expectoration continued in amounts varying from 30 to 60 cc. daily. On September 19th tartar emetic (2 per cent was given but discontinued after seven doses (41.5 cc.) because it was tolerated poorly and there was increase of cough. On October 29th emetine hydrochloride (0.06 Gm. daily) was started and completed November 5th. One day after onset of emetine therapy many tubercle bacilli were found in the sputum.

One week following the conclusion of emetine therapy there was definite improvement. The weight had increased 5 pounds, the cough was less frequent and chest pain had disappeared. Sputum had also decreased in amount but this was more clearly manifest at the end of another week; daily amounts varied from 4 to 20 cc. consisting principally of a thin watery fluid. Twelve sputum examinations (six concentrated) were negative thereafter for ova and tubercle bacilli.

Three weeks after completion of emetine therapy the patient was asymptomatic and his weight was 124 pounds. There was no change in the x-ray appearance of the chest from September 16th to November 16th.

CASE V. A nineteen year old Filipino male was admitted to an evacuation hospital February 26, 1945, complaining of cough and dyspnea. His present illness began in December, 1944, with loss of appetite, cough and weakness. These symptoms continued and gradually chest pain, aggravated by respiration, chilly sensations and dyspnea appeared. On the day of admission he became "very sick."

He had been a student prior to the invasion and joining the guerrillas he lived in the mountains of Leyte where he ate both raw and cooked crabs, crayfish and mud fish (alimongo and haloan). There was no family history of tuberculosis.

Physical examination showed a bilateral hydropneumothorax. The leukocyte count was 21,800 per cu. mm. with 72 per cent neutrophils, 19 per cent lymphocytes and 9 per cent eosinophils. Fifteen hundred cc. of greyish-green

purulent fluid was withdrawn from both right and left pleural cavities. The fluid was sterile after forty-eight hours and there were no organisms seen on smear. A sputum specimen contained tubercle bacilli. During the remainder of the observation fourteen subsequent specimens, six by concentrated technics, were negative. He was transferred and on March 7th another thoracentesis was done because of respiratory embarrassment, 500 cc. of greyish-yellow cloudy fluid containing mucopurulent particles being withdrawn from the right chest. This, too, proved sterile and a search for bacteria and parasites was negative. One week later thoracentesis was again necessary but only 200 cc. of greyish-yellow caseous material was withdrawn. Two weeks later, June 4th, 500 cc. of thick green purulent fluid was again aspirated and 75,000 units of penicillin were instilled. His condition thereafter improved, he became afebrile and was transferred here August 25, 1945.

Physical examination showed a thin young male, weight 118 pounds (normal 128 pounds), who appeared chronically ill. There were râles, dullness and diminished to absent breath sounds over both lower lobes. X-ray of the chest showed a hazy infiltration above the third rib anterior on the right. There was increased bronchovascular markings in each lung and pleural thickening along both lateral chest walls more marked at the bases. The hemoglobin was 95 per cent (Sahli) the erythrocyte count was 4,800,000 per cu. mm. leukocytes 15,800 per cu. mm. with 36 per cent neutrophils, 22 per cent lymphocytes and 42 per cent eosinophils. On September 10th a few ova of *P. westermani* were seen in the sputum but daily specimens for the next week were negative. On September 22nd ova of *P. westermani* were identified in the stool, in addition to ova of *T. trichiura*, hookworm and cysts of *E. nana*. The next day ova of *P. westermani* were found in the sputum. Tartar emetic therapy (2 per cent) was begun on September 10th but discontinued on September 26th (total of 54 cc.) because of reaction and apparent lack of response to the drug. On September 29th emetine hydrochloride (0.06 Gm. daily) was started. It was completed October 4th.

One week following conclusion of therapy his weight was 120 pounds, cough had decreased and mucopurulent sputum without trace of blood was present in lesser amounts. The patient

stated that although following thoracentesis he felt much better he thought that all his symptoms had been decreased following the taking of emetine. October 22nd, two and one-half weeks after emetine, an x-ray showed considerable resolution of the pulmonary infiltration in the first three interspaces on the right. On November 6th his weight was 128 pounds, cough was minimal and he was asymptomatic. One week later, November 13th, he was still asymptomatic; the temperature varied from 99° to 99.4°F., the sedimentation rate had risen to 33 mm. per hour and the quantity of sputum varied from 0 to 6 cc. daily. The x-ray of the chest showed no change in the basal pleural thickening and the infiltration in the right lung had completely resolved. Further sputum examinations were negative for ova.

CASE VI. A twenty-eight year old Filipino male was transferred to this hospital on August 25, 1945, from another institution where he had been hospitalized for two months.

His illness dated back to February, 1944, when he developed fever, chills and hemoptysis. He continued as a guerrilla in spite of these symptoms. Fever and chills disappeared in a few days but cough continued and became excessive at night, resulting in insomnia and loss of weight. Chest pain, aggravated by respiratory movement, appeared. The persistence of hemoptysis, recurrence of pain and constant fatigue finally made him seek medical attention in June, 1945. As a guerrilla he had eaten both raw and cooked fresh-water eel (*casili*), shrimp (*ulang*) and crab (*alimongo*). There was no family history of tuberculosis.

On examination June 22nd the temperature was 98.6°F. and râles and increased vocal fremitus were noted at the left apex. The sedimentation rate was 36 mm. per hour; the leukocyte count was 4,600 per cu. mm. with 43 per cent neutrophils, 46 per cent lymphocytes and 11 per cent eosinophils. An x-ray of the chest showed minimal infiltration with bronchial distribution in the left lower lung field which was interpreted as minimal pneumonitis. Sputum was negative for tubercle bacilli. His condition remained unchanged for the next two months. Cough and hemoptysis continued, the temperature remained normal (99.8° to 100°F. for only four days) and he was eventually transferred.

Physical examination on August 26, 1945, showed a well developed and nourished male,

weight 126 pounds (normal 138 pounds), temperature 98.8°F., pulse 80, respirations 20. There were a few scattered râles at both apices and increased vocal fremitus at the right base. An x-ray of the chest on August 28th revealed areas of patchy infiltration along the lateral portion of the right lung, more marked at the base; the left upper lobe was similarly involved and there was pleural thickening in both costophrenic sinuses. The x-rays were considered compatible with a diagnosis of paragonimiasis and a search for ova began. The sputum was negative previously on two occasions for tubercle bacilli. On October 16th sputum by concentration technic was negative for tubercle bacilli but contained ova of *P. westermani*. These findings were repeated the following day. On October 18th emetine hydrochloride (0.06 Gm. daily) therapy was started and completed October 26th. Following the fifth dose of emetine his condition was definitely improved. Cough lessened, pain and dyspnea disappeared, and sputum was markedly decreased in amount and altered in character from a blood-specked mucopurulent fluid to a thin watery saliva. Because of a leukocyte count of 10,400 with 51 per cent eosinophils he was proctoscoped. This procedure was entirely negative. Stools contained ova of *A. lumbricoides*, hookworm and *T. trichiura*. On November 18th his weight was 124 pounds; three weeks following the treatment with emetine he was asymptomatic. His daily measured sputum, principally saliva, did not exceed 8 cc. His last x-ray on November 16, 1945, showed clear lung fields.

CASE VII. A twenty-three year old Filipino guerrilla was first admitted to a field hospital June 1, 1945, because of hemoptysis. His illness began November, 1944, when he noted the onset of a nocturnal cough productive of very little sputum. One month later anterior chest pain, brought on by exertion, appeared and shortly afterward hemoptysis began, which continued for a month. Hematemesis on two or three occasions, night sweats and slight loss of weight were also present. Shortly after the Japanese invasion he had become a guerrilla and living in the mountains had eaten both raw and boiled fresh-water crayfish. There was no family history of tuberculosis.

Examination revealed evidences of slight loss of weight, weight 133 pounds, temperature 98.6°F., pulse 68, respirations 18 and blood pressure 100/64. There were moist râles and

diminished breath sounds in the right, middle and lower lobes.

An x-ray of the chest revealed multiple cavitation in the right lower lobe, surrounded by a large area of increased density. Hemoglobin was 80 per cent (Sahli) the erythrocyte count was 4,200,000 per cu. mm; the leukocyte count was 9,400 per cu. mm. with 45 per cent neutrophils, 24 per cent lymphocytes, 30 per cent eosinophils and 1 per cent monocytes. The sputum was negative for tubercle bacilli. The sedimentation rate was 39 mm. in one hour. Urinalysis was negative. Stool examination revealed ova of *A. lumbricoides*, *T. trichiura* and hookworm.

His condition remained unchanged in the next two and one-half months; the cough continued unabated and there was no loss of weight. He was afebrile except for a malarial episode at which time a blood smear revealed *Pl. vivax*. There was little change roentgenologically, the areas of cavitation were less distinct and the surrounding density was slightly increased.

On transfer to this hospital, August 28, 1945, the previously noted findings were confirmed. Proctoscopic examination revealed ulceration between the first and second folds although nine stool examinations were negative for amebae. A thoracentesis of the right chest yielded 5 cc. of sterile bloody fluid which did not contain ova or parasites. In view of the great likelihood that *E. histolytica* infection was present a course of emetine hydrochloride (0.06 Gm. daily) was given for eight days and completed September 28, 1945. There was no immediate effect but a gradual diminution of the cough and decrease in sputum were apparent. The sputum, however, remained purulent and it was still occasionally bloody one month later. The chest pain gradually disappeared and a weight gain of 7 pounds occurred. Tubercle bacilli were not present on nine sputum examinations. On October 29th, after four negative examinations, ova of *P. westermani* were found; eleven subsequent examinations were negative. Repeated x-ray examinations and fluoroscopy from June to November showed the spontaneous closure and disappearance of two cavities in the right middle lobe and the appearance and disappearance of a large cavity in the right lower lobe. On the final film November 17, 1945, there was moderate clearing of the surrounding density in the right middle and lower lobe.

CASE VIII. A thirty-nine year old Filipino male was admitted October 6, 1945, complain-

ing of fever, cough, hemoptysis and dull pain in the left calf and thigh. His illness dated back to July, 1945, when he developed chills and fever which was diagnosed clinically as malaria. He made a gradual recovery from this illness until August 15th when he began to spit blood like grains of rice. He became feverish but kept on working. The cough became constant and was especially marked in the evening and early morning. Following the onset of cough he noticed the appearance of anterior chest pain and an ache in the left calf and thigh. There was no malaise or weakness and he stated that if not for the cough he would feel well. He had lived in Mindanao and had been a Japanese prisoner until January 20, 1943. He frequently ate shellfish and fresh-water crabs (*alimongo*), both raw and cooked, but insisted that he had eaten none since May, 1942. His previous health was excellent. There was no family history of pulmonary tuberculosis.

Examination revealed a well developed male, temperature 98.6°F., pulse 72, respirations 18, blood pressure 106/66 and weight 118 pounds. There were medium moist râles at the right apex and scattered moist râles at both bases. The extremities were normal. Hemoglobin was 80 per cent, erythrocyte count 3,900,000 per cu. mm., the leukocyte count was 8,200 per cu. mm. with 49 per cent neutrophils, 32 per cent lymphocytes and 19 per cent eosinophils. The sedimentation rate was 54 mm. in one hour. The sputum was purulent and contained dark blood; tubercle bacilli were not present and many ova of *P. westermani* were seen. An x-ray of the chest showed striking accentuation of the peribronchial markings. Ten days later a new soft mottled area was present in the right first anterior interspace and a similar area was questionably present in the left mid-lung field. Emetine hydrochloride (0.06 Gm. daily) was given from November 5th to November 13th. During the short period of five weeks' observation there was no fever and the patient subjectively felt well. The cough was troublesome and productive of bloody, purulent sputum measuring 60 cc. daily. There was mild diffuse, shifting chest pain. The physical findings did not change. One week after emetine, although there was little objective change, the patient stated that he was better and his weight had increased to 122 pounds. There was no change in the chest pain, cough or amount of sputum. Ova were obtained on two occasions in the

sputum and stool during therapy and one day following. Two specimens were negative one week later. Eleven specimens, four by concentration technics, were negative for tubercle bacilli. An x-ray of the chest was unchanged one week following therapy.

CASE IX. A twenty year old Filipino male was admitted October 10, 1945, with a diagnosis of pleurisy with effusion.

His present illness began one year before with a constant nonproductive cough. Four months later he noted the appearance of small flecks of blood. In the next two months he developed marked weakness and anterior chest pain aggravated by respiratory movement. These symptoms continued unabated for three months when he developed fever, chills and dyspnea and was hospitalized at a guerrilla installation for one month. He lived in Mindanao, P.I. and had served as a guerrilla in the mountains of that island. He frequently ate fresh-water fish and shell-fish (alimongo, haloan and pasayan). He had been well except for five recurrences of malaria. There was no family history of tuberculosis.

He stayed in the guerrilla hospital for a month and was then transferred to an army hospital where he was found to have a right pyothorax. Four hundred cc. of thick creamy sterile fluid was withdrawn from the right chest September 20th. A centrifuged specimen of this fluid was negative for ova and parasitic cysts. Emetine hydrochloride (0.06 Gm. daily) was given for three doses in combination with penicillin, 25,000 units every four hours. There was no note on the chart to explain this treatment; presumably the pyothorax was thought to result from either paragonimiasis or amebic liver abscess. By September 30th he was much more comfortable, the chest pain had cleared, and the dyspnea was diminished although the physical signs were apparently unchanged. X-ray examination showed diminution of the fluid.

On admission he did not appear acutely ill. The physical signs of thickened pleura with fluid were evident. The hemoglobin content of the blood was 90 per cent, the erythrocyte count was 4,700,000 per cu. mm., the leukocyte count was 10,800 with 43 per cent neutrophils, 39 per cent lymphocytes and 18 per cent eosinophils. The sputum contained ova of *P. westermani* on four different days and was negative thereafter on ten occasions. The urinalysis was negative.

The Kahn test on two occasions gave a doubtful reaction and the Wassermann test was negative. The stool contained ova of *A. lumbricoides*, hookworm and *T. trichiura*.

Eight cc. of chocolate-red purulent fluid, containing yellowish curd-like material, was withdrawn from the right chest on November 7th. Microscopically this was composed of leukocytes in various stages of degeneration, red cells, epithelial cells and yeast forms; eosinophils were rare and ova of *P. westermani* were not seen. Treatment with emetine hydrochloride (0.04 Gm. daily) was started November 7th and completed November 18th.

During therapy his appetite decreased and he lost 5½ pounds of weight. This was regained within four days, at the conclusion of treatment. Near the end of therapy, November 15th, physical and x-ray examination showed no change. Following therapy he felt slightly better. The cough was less and there was striking diminution of sputum. Ova were not obtained by concentration technic in five specimens.

One week post-therapy, November 25th, the cough was non-productive and less frequent, chest pain and dyspnea were gone, and it was noted that hemoptysis had been absent for over two weeks. The signs of thickened pleura and fluid were still persistent.

CASE X. A twenty-seven year old Filipino male was admitted to this hospital with a diagnosis of paragonimiasis on October 10, 1945.

He had been hospitalized in several institutions since June 9, 1945. As a guerrilla in the mountains of Mindanao he had eaten fresh-water crabs, raw and semi-cooked, in June, 1944. There was no family history of pulmonary tuberculosis. About September, 1944, he noted the onset of non-productive cough. This persisted, and early in February, 1945, dyspnea, anterior chest pain and speckled bloody sputum appeared and gradually increased in severity. In June hemoptysis prompted him to enter a hospital.

On admission he was acutely ill, dyspneic, coughing frequently but afebrile. He had signs of bilateral effusion. The hemoglobin content of the blood was 100 per cent (Sahli), erythrocyte count was 5,400,000 per cu. mm., the leukocyte count was 21,000 with 64 per cent neutrophils, 21 per cent lymphocytes and 15 per cent eosinophils. Multiple thoracentesis in the course of several days yielded 2,500 cc. from the right and 2,000 cc. from the left pleural cavity, an

opalescent yellow fluid containing yellow flaky material. Ova of *P. westermani* were found in the fluid repeatedly. He was given a course of emetine hydrochloride, total dosage 0.66 Gm. from June 12th to June 22nd, and on June 25th emetine 0.03 Gm. was injected into each pleural cavity. Between July 13th and the 21st he received 0.54 Gm. of this drug again, intramuscularly, and on July 4th 0.04 Gm. was instilled into each pleural cavity following thoracentesis. On July 21st the fluid was less in amount and clearer, which led to the belief that loculation was present. Ova were still noted in the pleural fluid bilaterally but were infrequent and required a more diligent search for demonstration. The sputum had decreased from 120 cc. to 15 cc. daily. It contained ova only in one specimen (June 25th) and was negative on five occasions. The general improvement was definite.

He was transferred to still another hospital September 9th and at this institution signs of a moderate amount of fluid were still present. A leukocyte count was 8,400 per cu. mm. with 54 per cent neutrophils, 28 per cent lymphocytes and 18 per cent eosinophils. The sputum was negative for tubercle bacilli and ova. On September 17th, 600 cc. of cream-colored, thick fluid containing ova was obtained from the right chest. During this period weakness, anorexia and anterior chest pain were prominent. Another course of emetine was given (0.06 Gm.) between September 19th and September 27th. His last thoracentesis was done September 30th and 200 cc. of fluid, identical with that removed September 17th, was obtained from the left chest. It, too, contained ova of *P. westermani*. Following this procedure there was steady, gradual and consistent improvement. His complaints disappeared and the physical signs diminished. On arrival at this hospital he had evidence only of thickened pleura at the right base. Sputum was obtained with difficulty for examination. A total of eleven examinations (seven concentrated) were negative for tubercle bacilli. Ten additional examinations were negative for ova of *P. westermani*. The urinalysis was negative. The sedimentation rate was 11 mm. in one hour. The Kahn test was negative. The stool contained ova of *A. lumbricoides*, *S. stercoris* and hookworm. An x-ray of the chest, November 15th, showed bilateral pleural thickening at the base. There was no evidence of pulmonary infiltration. There

were no complaints throughout his hospital stay in October and November.

CASE XI. A twenty-eight year old Filipino male was transferred from another hospital October 9, 1945, with a diagnosis of pulmonary tuberculosis.

His illness had started in January, 1943, with a constant cough productive of thick, yellow sputum. The cough continued for a year during which time he lost some weight. He then noted chest pain only with cough, dyspnea on exertion and easy fatigability. In April, 1945, following severe cough, he vomited about a small cupful of blood; since then his cough was constantly productive of rice grain specks of blood.

He had been a guerrilla in Mindanao. He denied the intake of fresh-water shellfish or fish and insisted he had eaten only sea food. There was no family history of tuberculosis. Physical examination at the previous hospital, July 13, 1945, revealed that he was well developed and well nourished and did not appear ill. There were fine inconstant râles in both lower lobes and increase of spoken voice in the left upper lobe. A chest x-ray the following day showed extensive pulmonary infiltration at the level of the first, second and third anterior interspaces on the right, and at the second and third interspaces on the left. As a result of the x-ray report extensive sputum examinations were done but twenty-three specimens were negative for tubercle bacilli. During his hospital stay the temperature, normal for several weeks at a time, would rise to 101° and 102°F. for two or three days. He felt well, his appetite was good and the cough was moderate with little expectoration.

At this hospital, October 15, 1945, physical examination disclosed medium moist râles at both apices and the left base. His weight was 114 pounds (normal weight was 118 pounds). After one negative sputum examination on October 29th ova of *P. westermani* were recovered and this was verified on five other occasions in the next two weeks. Eleven specimens, six by concentration, were negative for tubercle bacilli. The hemoglobin of the blood was 95 per cent (Sahli) erythrocytes 5,000,000 per cu. mm., the leukocyte count was 10,500 with 48 per cent neutrophils, 37 per cent lymphocytes and 13 per cent eosinophils. A sedimentation rate was 30 mm. per hour. Stools contained ova of hookworm and *T. trichiura*. The urinalysis was negative.

In the next few weeks his cough continued

sputum and stool during therapy and one day following. Two specimens were negative one week later. Eleven specimens, four by concentration technics, were negative for tubercle bacilli. An x-ray of the chest was unchanged one week following therapy.

CASE IX. A twenty year old Filipino male was admitted October 10, 1945, with a diagnosis of pleurisy with effusion.

His present illness began one year before with a constant nonproductive cough. Four months later he noted the appearance of small flecks of blood. In the next two months he developed marked weakness and anterior chest pain aggravated by respiratory movement. These symptoms continued unabated for three months when he developed fever, chills and dyspnea and was hospitalized at a guerrilla installation for one month. He lived in Mindanao, P.I. and had served as a guerrilla in the mountains of that island. He frequently ate fresh-water fish and shell-fish (alimongo, haloan and pasayan). He had been well except for five recurrences of malaria. There was no family history of tuberculosis.

He stayed in the guerrilla hospital for a month and was then transferred to an army hospital where he was found to have a right pyothorax. Four hundred cc. of thick creamy sterile fluid was withdrawn from the right chest September 20th. A centrifuged specimen of this fluid was negative for ova and parasitic cysts. Emetine hydrochloride (0.06 Gm. daily) was given for three doses in combination with penicillin, 25,000 units every four hours. There was no note on the chart to explain this treatment; presumably the pyothorax was thought to result from either paragonimiasis or amebic liver abscess. By September 30th he was much more comfortable, the chest pain had cleared, and the dyspnea was diminished although the physical signs were apparently unchanged. X-ray examination showed diminution of the fluid.

On admission he did not appear acutely ill. The physical signs of thickened pleura with fluid were evident. The hemoglobin content of the blood was 90 per cent, the erythrocyte count was 4,700,000 per cu. mm., the leukocyte count was 10,800 with 43 per cent neutrophils, 39 per cent lymphocytes and 18 per cent eosinophils. The sputum contained ova of *P. westermani* on four different days and was negative thereafter on ten occasions. The urinalysis was negative.

The Kahn test on two occasions gave a doubtful reaction and the Wassermann test was negative. The stool contained ova of *A. lumbricoides*, hookworm and *T. trichiura*.

Eight cc. of chocolate-red purulent fluid, containing yellowish curd-like material, was withdrawn from the right chest on November 7th. Microscopically this was composed of leukocytes in various stages of degeneration, red cells, epithelial cells and yeast forms; eosinophils were rare and ova of *P. westermani* were not seen. Treatment with emetine hydrochloride (0.04 Gm. daily) was started November 7th and completed November 18th.

During therapy his appetite decreased and he lost 5½ pounds of weight. This was regained within four days, at the conclusion of treatment. Near the end of therapy, November 15th, physical and x-ray examination showed no change. Following therapy he felt slightly better. The cough was less and there was striking diminution of sputum. Ova were not obtained by concentration technic in five specimens.

One week post-therapy, November 25th, the cough was non-productive and less frequent, chest pain and dyspnea were gone, and it was noted that hemoptysis had been absent for over two weeks. The signs of thickened pleura and fluid were still persistent.

CASE X. A twenty-seven year old Filipino male was admitted to this hospital with a diagnosis of paragonimiasis on October 10, 1945.

He had been hospitalized in several institutions since June 9, 1945. As a guerrilla in the mountains of Mindanao he had eaten fresh-water crabs, raw and semi-cooked, in June, 1944. There was no family history of pulmonary tuberculosis. About September, 1944, he noted the onset of non-productive cough. This persisted, and early in February, 1945, dyspnea, anterior chest pain and speckled bloody sputum appeared and gradually increased in severity. In June hemoptysis prompted him to enter a hospital.

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In the next few weeks his cough continued

unabated. The chest pain which was not affected by respiratory movement was mild and bilateral and principally confined to the anterior chest. The sputum was greenish-yellow, thin and purulent, reaching 90 cc. daily and rarely contained bloody tobacco-like shreds. During emetine hydrochloride administration (0.06 Gm. daily) from November 6th to 13th, the cough diminished and the pain lessened. The sputum disappeared and only saliva was obtained; however, ova were present for one day after the conclusion of therapy. On November 21st there was no change in the physical signs or x-ray appearance of the lung.

CASE XII. A thirty-four year old Filipino male was admitted October 9, 1946, with a diagnosis of paragonimiasis and pulmonary tuberculosis. His present illness dated back to December, 1942, when, following malaria, he developed a cough, bilateral chest pain aggravated by respiratory motion, dyspnea and weakness. Although he lived in Leyte, P.I., he had joined the guerrillas in Mindanao in August, 1943. He liked shellfish and fish and had eaten them in quantity, both raw and cooked, prior to his illness. As a guerrilla he ate fresh-water crab (alimango), mudfish (haloan) shrimp (ulang). There was no family history of tuberculosis. Shortly after becoming a guerrilla his symptoms became more severe and vomiting occurred in the morning. His cough became productive, night sweats appeared and loss of weight and asthenia resulted. He was in and out of hospitals for the next two years. In January, 1945, he spit up blood and hemoptysis had recurred intermittently since then.

Notes were not available until he was admitted to a hospital, August 29, 1945, where it was stated that he was in his seventh month of hospitalization. Examination disclosed soft, bubbling râles throughout both lungs. An x-ray of the chest was interpreted as indicative of far advanced tuberculosis with cavitation. He was transferred to another hospital one week later where it was noted that his temperature was 98.6°F. and that he did not appear ill. Physical examination of the chest showed many fine râles throughout both lung fields together with marked diminution of breath sounds. A leukocyte count was 15,400 per cu. mm. with 48 per cent neutrophils, 20 per cent lymphocytes and 32 per cent eosinophils. Ova of *P. westermani* were found frequently in the sputum. On one

occasion, September 29, 1945, a few acid-fast bacilli were seen. Thereafter a total of twenty-four specimens were examined from September 9th to October 6th, and five specimens by concentration technics were examined from October 19th to November 12th but tubercle bacilli were not found again. A chest x-ray was similarly interpreted as indicative of far advanced tuberculosis with cavitation. He was placed on emetine hydrochloride (0.06 Gm. daily) October 4th for six days and transferred to this hospital.

On admission he complained of bilateral chest pain, cough and dyspnea. The findings of the physical examination were confirmed. The sputum was yellowish-white, purulent and streaked with minute bloody shreds. The hemoglobin content of the blood was 75 per cent and the erythrocyte count was 3,900,000 per cu. mm. The sedimentation rate was 55 mm. in one hour. Urinalysis and Kahn test were negative. The stool contained ova of *A. lumbricoides*, hookworm and cysts of *E. nana*. His condition remained unchanged until October 17th when his temperature rose suddenly to 101°F. simultaneously with increase of cough, chest pain and respiratory rate. Physical examination did not explain this episode but sulfadiazine therapy resulted in a normal temperature within two days. Emetine hydrochloride (0.06 Gm. daily) was started the night of October 19th and continued until October 26th. One week later the cough was much improved. There was only occasional left-sided pain, the dyspnea was moderate and medium moist râles were scattered throughout both lungs. His weight, 135 pounds, was only 5 pounds under normal. A tuberculin test (P.P.D.) was negative in the first strength and weakly positive in the second. In the next three weeks his course seemed one of very slow but steady improvement. On November 20th he was afebrile, hemoptysis had been absent for a month although the cough was still severe and productive of about 12 cc. of yellow purulent sputum daily. Chest pain was still present and he appeared ill. The x-ray findings of the chest were unchanged.

SUMMARY

1. Paragonimiasis was encountered in the Philippine Islands among guerrillas hospitalized for observation of tuberculosis.

Twelve cases were found among approximately 250 patients.

2. Coexistent tuberculosis and paragonimiasis were established in four of the twelve cases reported.

3. Paragonimiasis may simulate tuberculosis closely so that the former should be considered in the differential diagnosis of hemoptysis in personnel who have been in endemic regions.

4. Emetine hydrochloride relieved subjective symptoms of paragonimiasis promptly but it had only a slight effect on the pulmonary disorder as indicated by x-ray findings in the period of our observations.

5. Paragonimiasis may produce serum protein changes and transiently positive serologic tests for syphilis.

6. Treatment of this disease is still far from satisfactory and more efficient therapeutic agents are required.

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Studies on Patients with Cirrhosis of the Liver*

Plasma and Liver Lipid Distribution and Its Relation to the Pathology of the Liver

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IT is generally agreed that the concentration and nature of fatty acids in the liver vary greatly in health and disease.¹ Changes are most marked when the liver itself is the site of the pathologic disorder.^{2,3} Because of its importance in the metabolism of lipids, any disease of the liver will inevitably affect the pattern of the plasma lipids. During the past few years we have determined the plasma lipids in a group of patients with clinical evidences of liver disease, particularly cirrhosis of the liver, who later came to postmortem. We were, therefore, able to determine the liver lipids and to examine the state of the liver, thus making it possible to correlate plasma and liver lipids with the pathologic state of the liver. In some of the patients the vitamin A and carotene levels of the plasma and liver were also determined. Both of these substances are fat soluble and are present normally in the liver in considerable concentrations.^{4,5}

All of the twenty-one subjects were patients on the wards of the Third (New York University) Medical Division, Bellevue Hospital. They were adults, their ages varying from twenty-one to seventy-four years; nine were females. Table I summarizes the clinical and laboratory findings other than the lipid, vitamin A and carotene determinations. All but three of the patients gave histories of alcoholism extending over a period of years. Cases 1 and 2 were not alcoholics and Case 13, who had diabetes mellitus, gave a history of limited alcohol intake. The clinical diagnosis of cirrhosis

of the liver was made in all but Cases 1 and 2. Twelve of the patients were in poor nutritional state which in six cases had advanced to a state of emaciation. Of the nineteen patients with cirrhosis, 16 had ascites and 15 were jaundiced. As is to be expected, the albumin-globulin ratio was inverted in all of the patients with cirrhosis and the albumin levels were below the normal value.

The lipid values of the plasmas and livers are reported in Table II. The methods used for their determination have been reported previously.^{6,7} The pathologic state of the liver is described in Table II in order to permit correlation with the lipid analyses. Protocols of the cases give the details. In order to facilitate discussion of the results the cases are divided into three groups: (1) those patients in whom there was an increase in the plasma lipids; (2) those patients with an increase in liver lipids and (3) patients in whom the only change was in the ratio of free to total cholesterol in the plasma. The relation of plasma to liver lipids is shown graphically for each group.

Group 1—Plasma Lipids Elevated. There were seven (Cases 1, 3, 4, 12, 13, 16 and 20) in whom the total plasma lipids were elevated. (Fig. 1.) This increase was shared by the other lipid fractions of the plasma with the exception of the total cholesterol which was not elevated in every case. In three (Cases 3, 4 and 16) the increase in plasma lipids was associated with a marked increase in liver lipids. In the livers, however, neither phospholipid nor total cholesterol fractions were involved in this

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increase. This is shown very clearly in the illustration. For comparison normal lipid values for both plasma and liver are given in Figure 3. The fact that the increase in plasma lipids was not associated with a consistent change in the concentration of liver

syphilis and a positive Wassermann reaction. In Case 12 the plasma sample was taken seven days before death when the patient was still able to eat. Four days before death he became seriously ill and was unable to eat regularly. It may well be

TABLE I

Case No.	Sex	Age	State of Nutrition	Alcohol Intake	Duration of Liver Symptoms	Ascites	Jaundice	Spider Angiomas	N.P.N. (mg. %)	Albumin Globulin (Gm. %)	Total Protein (Gm. %)	Hematocrit (%)	Icteric Index	Bromsulphalein (%)	R.B.C. (millions)
1	M	52	Emac.	None	4 wk.	Moderate	Deep	No	5.4
2	F	54	Good	None	1 day	No	Deep	No	60-211	55	2.1
3	M	50	Good	30 yr.	2½ wk.	Yes	Deep	No	32	2.0/1.7	3.7	150	2.5
4	M	47	Obese	7 yr.	4 days	Severe	Deep	No	75	2.2/2.5	4.7	135	4.4
5	F	49	Emac.	3 yr.	2 wk.	Severe	Deep	No	30	10	2.0
6	F	24	Emac.	5 yr.	8 mo.	Severe	Deep	Yes	33-71	40	1.8
7	F	39	Emac.	Years	8 mo.	Yes	No	30-53	3.0/4.1	7.1	21	3.7
8	F	71	Emac.	Years	2+ yr.	Yes	Deep	No	32	2.2/3.9	6.1	60	4.3
9	M	40	Obese	10 yr.	9 days	Yes	Deep	Yes	32	2.7/4.0	6.7	70	3.4
10	M	50	Obese	Years	1 yr.	No	Yes and No	No	31	12	2.0
11	M	52	Emac.	Years	1 yr.	Severe	Yes	No	30-71	1.9/4.4	6.3	21	3.4
12	M	61	Fair	Years	4 wk.	Yes	No	No	34	3.0/4.2	7.2	25	4.5
13	M	49	Fair	Slight	2 yr.	Slight	Moderate	Yes	66	3.2/4.2	7.2	23	16	4.0
14	M	45	Poor	26 yr.	4 wk.	Yes	Yes	No	24-61	2.7/4.4	4.5	39	72-30	3.2
15	M	67	Poor	25 yr.	4 wk.	Yes	No	No	31-25	2.0/3.0	5.0	33-38	11	29-46	3.3
16	F	45	Poor	Years	3 mo.	No	Yes	No	19-63	2.5/3.0	5.5	27-22	1.5
17	M	61	Poor	21 yr.	2 yr.	Yes	No	No	30-67	1.4/4.6	5.5	39	16-24	44	3.6
18	F	57	Good	Years	4 wk.	Yes	Yes	No	30-55	1.8/4.5	6.3	39	25	42-28	3.4
19	F	50	Poor	Years	6 mo.	No	Yes	No	16	1.7/5.0	6.7	32	25	29	3.4
20	F	35	Poor	Years	2 yr.	Slight	No	32	1.8/4.7	6.5	33	35	18	3.0
21	M	60	Good	Years	18 mo.	Yes	Yes	No	43	1.9/4.3	6.2	26	23	3.8

lipids may have been due to the character of the pathologic change in the liver. For example, in Cases 1 and 13 the livers were both the seat of malignant changes, and in Case 1 this was so severe that there was practically no normal liver tissue left. It is interesting in this case that in spite of the widespread cellular change in the liver the ratio of free to total cholesterol in the plasma was normal. In the entire group of patients this was the only case in which this occurred. Case 13 was complicated by diabetes mellitus and, although this is often associated with fatty infiltration of the liver, in this patient there was no increase in liver lipids. In the other two cases in group 1, the liver in Case 20 was the seat of two pathologic processes and was grossly deformed. The left lobe showed the changes characteristic of portal cirrhosis and the right lobe was divided into several lobes by bands of fibrous tissue and was diagnosed as *hepar lobatum*. The patient had a history of

that the fat content of the liver decreased during this time and that the interval between the plasma and liver sample accounts for the lack of correlation between the lipid concentrations.

Group 2—Increase in Liver Lipids. The total fatty acids were greatly increased in the livers of Cases 3, 4, 5, 9 and 16. (Fig. 2.) In each case both the total fatty acids and the neutral fat fraction of the liver lipids increased. The phospholipids, however, were within normal limits, never exceeding 2.1 Gm. per cent. It is interesting that the phospholipid fraction was not affected in spite of the tremendous increase in total lipids. Examination of the plasma lipids of the five patients shows that the total fatty acids were elevated in only three (Cases 3, 4 and 16). Again, as in group 1, all of the lipid fractions of the plasma shared in the increase and the phospholipids were 260 mg. per cent or more. In Case 9, although the total plasma fatty acids were within the

TABLE II

Case No.	Days before Death	Blood Plasma Lipids							Liver Lipids							Histologic Findings in Liver	
		Total Lipids (mg. %)	Total Fatty Acids (mg. %)	Neutral Fat (mg. %)	Phospholipids (mg. %)	Cholesterol				Liver Weight (Gm. %)	Total Lipids (Gm. %)	Total Fatty Acids (Gm. %)	Neutral Fat (Gm. %)	Phospholipids (Gm. %)	Cholesterol		
						Total (mg. %)	Esters (mg. %)	Free (mg. %)	Free Ratio						Total (Gm. %)		Free (Gm. %)
1	4	1108	718	409	259	281	224	57	20	4030	3.02	2.14	1.00	1.73	0.251	0.20	Liver architecture obscured by loosely arranged small cell (lymphocytic) lymphosarcoma; extensive fatty change in liver cords and radiating bands of connective tissue
2	5	548	397	260	197	87	35	52	60	1800	2.94	2.02	0.78	1.88	0.251	0.21	The liver parenchyma is well preserved; no evidence of cirrhosis, no intrahepatic bile stasis, fatty deposits or inflammatory reaction
3	16	1428	886	500	618	310	9	301	97	2990	12.8	11.20	10.2	1.97	0.490	0.26	Mild monolobular type of portal cirrhosis with extensive fatty infiltration and focal evidence of bile stasis; there is focal necrosis of the fatty cells
4	1	709	486	327	261	121	4	117	97	4000	15.5	14.00	13.8	1.26	0.360	0.26	Extensive fatty infiltration with early monolobular cirrhosis; widespread focal necrosis of fatty cells
5	10	247	150	51	145	46	8	38	83	1600	26.4	24.50	24.5	1.59	0.252	0.17	Advanced monolobular cirrhosis with extensive fatty changes
6	21	693	416	237	212	194	81	113	60	1700	3.98	3.00	1.68	2.00	0.263	0.21	Advanced mono- and multilobular cirrhosis; some islands of liver tissue show considerable fatty change, others little or none; there is focal necrosis in the areas of advanced fatty changes
7	15	444	278	157	131	114	59	55	48	1150	3.79	2.78	1.57	1.94	0.280	0.25	Advanced multi- and monolobular cirrhosis with minimal fatty changes
8	14	391	220	70	176	109	51	58	53	940	3.19	2.36	1.43	1.41	0.290	0.20	Advanced cirrhosis with a necrotic undifferentiated carcinoma
9	6	492	290	90	237	150	22	128	85	4000	14.7	13.1	13.10	1.24	0.290	0.16	Fatty cirrhosis, monolobular type; extensive fatty changes in liver cords and in radiating bands of connective tissue extending around portal areas and into and around lobules
10	1	200	121	56	79	50	36	47	57	3070	3.43	2.40	1.01	2.11	0.280	0.24	Advanced multi- and monolobular cirrhosis with moderate fat deposits
11	40	330	201	94	127	83	29	53	65	1320	3.49	2.46	1.02	2.20	0.250	0.22	Moderate multi- and monolobular cirrhosis with moderate fat deposits and severe focal necrosis of fatty cells
12	7	862	616	457	204	162	85	77	48	1340	5.66	4.10	4.00	1.22	0.300	Advanced multi- and monolobular cirrhosis with minimal fatty changes
13	0	1384	868	472	541	314	180	234	75	3800	3.76	2.50	1.09	2.22	0.310	Liver cell type of carcinoma arising in advanced multilobular cirrhosis with practically no fatty change in surviving parenchyma
14	41	517	306	124	240	125	40	85	68	1450	4.78	3.60	2.45	1.90	0.290	Advanced multi- and monolobular cirrhosis with extensive necrosis and some focal fatty change

TABLE II.—(Continued)

Case No.		Blood Plasma Lipids										Liver Lipids						Histologic Findings in Liver	
		Total Lipids				Phospholipids (mg. %)	Cholesterol			Liver Weight (Gm. %)	Total Lipids Gm. %	Total Fatty Acids (Gm. %)	Neutral Fat (Gm. %)	Phospholipids (Gm. %)	Cholesterol				
		Total (mg. %)	Total Fatty Acids (mg. %)	Neutral Fat (mg. %)	Esters (mg. %)		Free (mg. %)	Free Ratio Total	Total (Gm. %)						Free (Gm. %)				
Days before Death		15	118	488	288	89	209	129	86	43	33	Moderate multi- and monolobular cirrhosis with minimal fat deposits; occasional portal area shows mononuclear cellular infiltration; slight bile duct proliferation
			91	137	88	49	36	
			81	155	98	57	37	
			59	148	88	50	34	
			20	492	268	57	216	150	87	53	35	
			0	380	252	58	179	103	55	48	46	0.240	...	
		16	24	1461	880	387	732	318	34	284	89	Extensive fatty change; mild monolobular cirrhosis with considerable loss of nuclear detail
			15	316	41	275	87	
			0	1397	880	482	587	297	44	253	85	0.380	...
		17	52	493	260	52	203	162	107	55	35	Advanced multilobular cirrhosis; no fatty changes
			24	163	105	58	36	
			7	129	79	50	38	0.250	...
		18	77	450	264	108	159	128	77	51	39	Advanced multilobular cirrhosis; practically no fatty change
			45	159	100	59	37	
			18	177	119	58	33	0.370	...
		19	6	541	300	97	213	165	93	72	44	0.330	...
												Advanced multilobular cirrhosis with islands of surviving hypertrophic liver cords with minimal fatty change
		20	254	424	232	45	190	127	87	40	31	Two findings in liver—advanced portal cirrhosis in left lobe and hepar lobatum in right lobe
			10	80	55	25	31	
			1	589	428	286	175	88	56	32	36	
		21	43	200	119	81	41	Advanced multilobular cirrhosis with practically no fatty change; there is considerable focal necrosis
			15	200	111	89	45	
			3	412	266	35	148	189	113	76	41	0.260	...

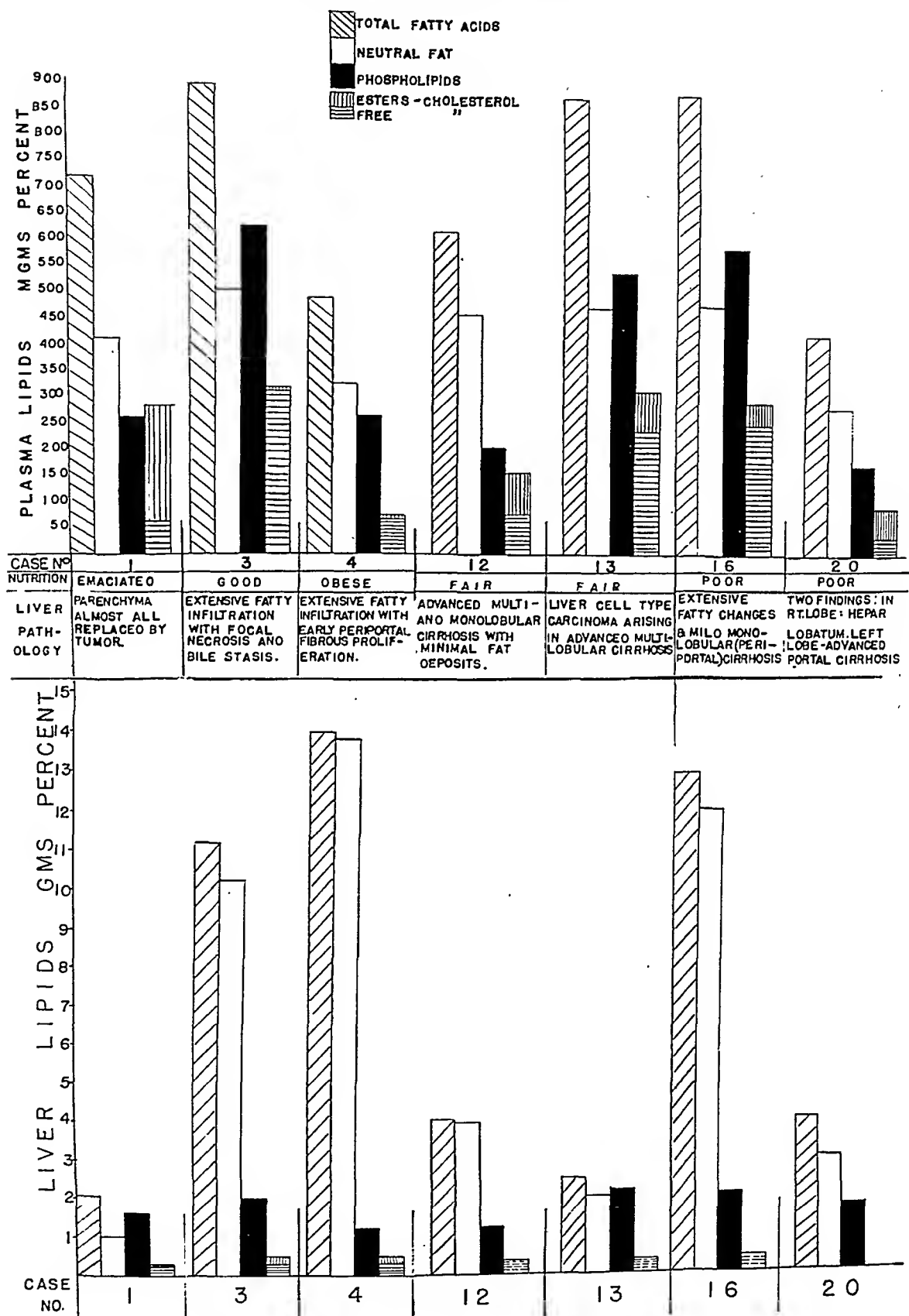


FIG. 1. Cases grouped according to increase in the plasma lipids.

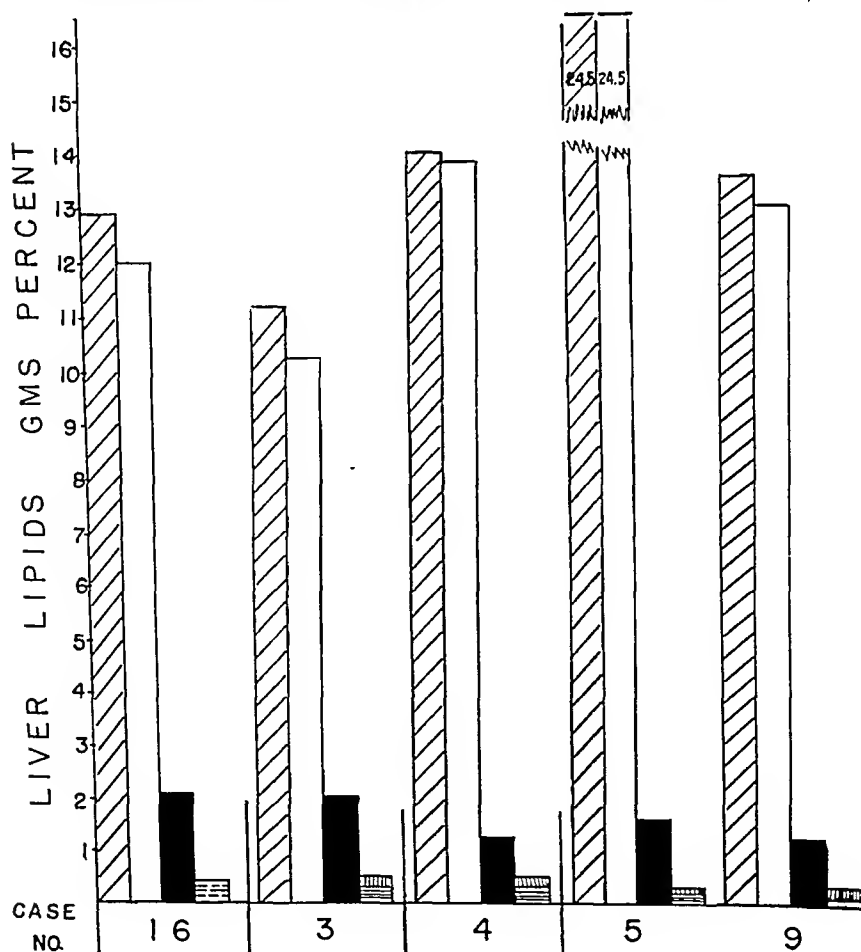
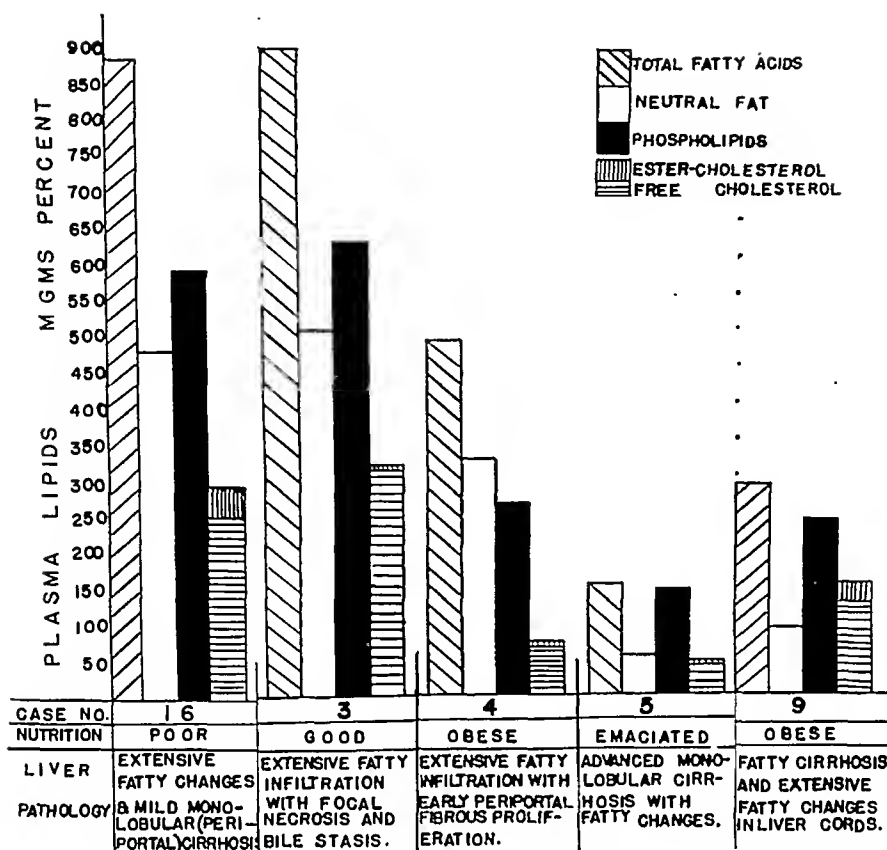


FIG. 2. Cases grouped according to increase in the liver lipids.

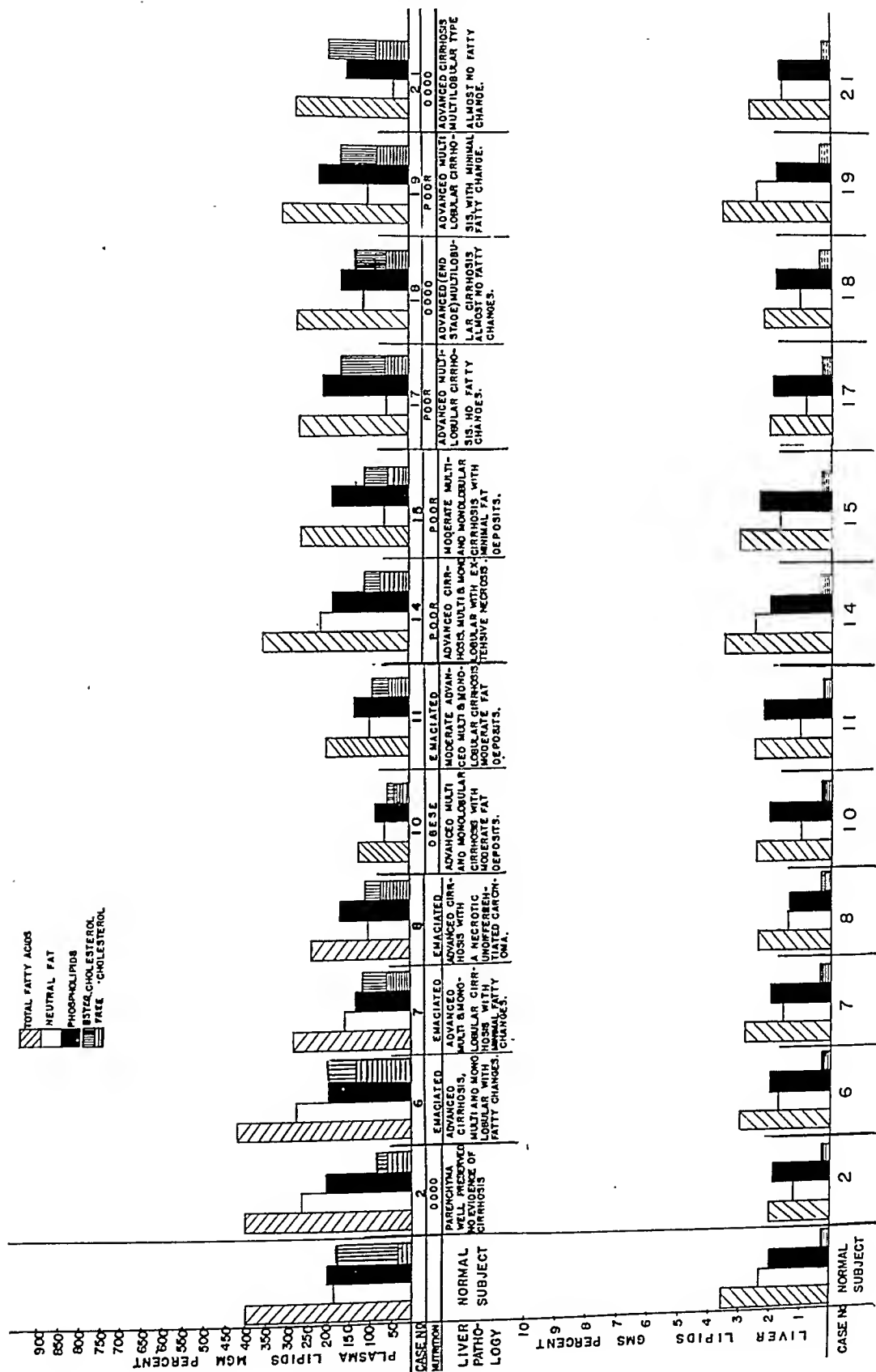


Fig. 3. Cases in which the only lipid change was in the ratio of free to total cholesterol in the plasma.

normal level, the phospholipid fraction was elevated (237 mg. per cent). In Case 5 there was no reflection in any fraction of the plasma lipids of the tremendous increase in liver lipids. Pathologically all of the livers showed extensive fatty changes and with the

In twelve patients the only striking change was in the ratio of free to total cholesterol. As we have previously reported, the ratio of free to total cholesterol in normal subjects does not exceed 29 per cent.⁸ In all of the patients in this study, with the exception

TABLE III
RELATION OF LIVER LIPIDS TO WET AND DRY WEIGHTS IN SIX CASES

Case No.	Liver Weight (Wet) Gm.	Water (%)	Wet Weight (Gm. %)							Total Lipids Gm. per Liver Wet Weight	Liver Weight (Dry) Gm.	Dry Weight (Gm. %)						
			Total Fatty Acids	"Neutral Fat"	Phospholipids	Cholesterol Total	Cholesterol Free	Cholesterol (% free)	Total Lipids			Total Fatty Acids	"Neutral Fat"	Phospholipids	Cholesterol Total	Cholesterol Free	Total Lipids	
1	4030	75.6	2.1	1.00	1.73	0.25	0.20	80.0	3.02	121.7	983.3	8.6	4.09	7.1	1.02	0.82	12.4	
3	2990	68.2	11.2	10.2	1.97	0.49	0.26	53.6	12.8	383.3	950.8	35.3	32.1	6.2	1.54	0.82	40.3	
4	4000	66.9	14.0	13.8	1.26	0.36	0.26	72.2	15.5	619.6	1324.	42.0	41.4	3.8	1.08	0.78	46.8	
5	1600	54.5	24.5	24.5	1.59	0.25	0.17	68.0	26.4	422.4	728.	53.9	53.9	3.5	0.55	0.37	58.0	
6	1700	78.3	3.0	1.68	2.0	0.26	0.21	80.8	3.98	67.7	368.9	13.8	7.8	9.2	1.2	0.97	18.3	
9	4000	70.0	13.6	13.1	1.24	0.29	0.16	55.2	14.7	587.2	1200.	45.3	43.6	4.1	0.97	0.53	48.9	

exception of Case 3 there were varying degrees of periportal cirrhosis. The nutritional status of the subjects was either good or obese in three (Cases 3, 4 and 9) but very poor in Cases 5 and 16. In this as in the previous group, one again encounters cases in which the changes in plasma and liver lipids do not parallel one another; in some cases in this group liver lipids were increased without any increase in plasma lipids. The time relation of the plasma sample to the liver sample varied from the day of death (Case 16) to ten days before death (Case 5). The latter case in which the liver lipid was the highest of any in the series, and in which the only alteration in plasma lipids was in the ratio of free to total cholesterol, was a patient who had been on an inadequate diet for six months prior to admission and who was emaciated. The fatty liver in this case therefore may have reflected the state of starvation, for experimentally starvation is associated with a decrease in plasma fatty acids rather than in increase.

Group 3—The Only Lipid Change Was in the Ratio of Free to Total Cholesterol in the Plasma.

of Case 1, this ratio was above normal and in the patients in group 3 this was the only significant change. The total liver lipids in this group of patients were within normal limits. With the exception of Case 2 these patients all had varying degrees of periportal cirrhosis and the pathologic findings were so consistent that the microscopic sections from case to case revealed only the differences in degree of the process. The liver in Case 8 was also the seat of an undifferentiated carcinoma but, unlike Case 13, this did not affect the level of the plasma lipids. It should be recalled that in Case 13 diabetes mellitus was also present.

It is obvious from the results that absolute correlation between plasma and liver lipid fractions does not always occur in disease of the liver. One fact stands out in all of the plasma determinations, namely, that in cirrhosis and in fatty infiltration of the liver the ratio of free to total cholesterol is abnormal, and this occurs regardless of the level of the total cholesterol. This finding was so uniform that we believe the diagnosis of cirrhosis of the liver, with or without fatty infiltration, should not be made when

the ratio of free to total cholesterol is within normal limits. According to the method we have reported and according to the reports of Sperry,^{8,9} this ratio normally does not exceed 29 per cent.

In six of the cases the per cent water

hauser's figures. In the liver of Case 5, however, there was an apparent complete lack of cephalin. Since the calculation of cephalin is indirect and is largely contingent upon the accuracy of the choline determination, the latter was carefully

TABLE IV
PARTITION OF PHOSPHOLIPIDS IN FOUR CASES

Case No.	Choline (mM %)	Phosphorus (mM %)	Choline Phosphorus	Phospholipids Total (Gm. %)	Sphingomyelin (Gm. %)	Mono Amino Phospholipids (Lecithin, Cephalin) (Gm. %)	Mono Amino Phospholipids (% of total)	Lecithin and Sphingomyelin (% of total phospholipids)	Cephalin (% of total phospholipids)	Sphingomyelin (% of total phospholipids)	Lecithin (% of total phospholipids)
4	1.04 *	1.56 *	.67 *	1.26 *	67.0 *	33.0 *	†	(63.0)
5	1.57	1.52	1.03	1.23	0.044	1.19	96.8	100.0	0.0	3.2	96.8
6	1.70	2.39	.71	1.92	0.091	1.83	95.3	71.0	29.0	4.7	66.3
9	1.04	1.55	.67	1.24	0.066	1.17	94.7	67.3	32.7	5.3	62.0

All values are expressed on basis of wet weights.

* Analysis done on petroleum ether extract of lipid fraction.

Lecithin and sphingomyelin per cent of total phospholipid, calculated from choline phosphorus ratio.

Cephalin per cent of total phospholipid, calculated from choline phosphorus ratio.

Sphingomyelin per cent of total phospholipid, calculated from diaminophospholipid.

Lecithin per cent of total phospholipid, calculated from monophospholipid and choline phosphorus ratio.

† On assumption that sphingomyelin constitutes about 4 per cent of the phospholipids in this liver. Thannhauser.^{10,11}

of the liver was determined (1, 3, 4, 5, 6 and 9, Table III) and the lipid concentration was calculated on the basis of the dry weight of the liver. On the basis of the dry weight each fraction naturally was more concentrated, and the results show that when an increase in the total lipids and their fractions occurred it was an absolute increase. The relationship of the lipid fractions to one another remained unchanged.

Partition of the phospholipids (Table IV) was done in four of the livers (Cases 4, 5, 6 and 9) according to the method of Thannhauser et al.¹⁰ In three of the four cases relative concentrations of lecithin, cephalin and sphingomyelin were very similar to those given by Thannhauser et al.¹¹ who reported an average distribution of 49, 47 and 4 per cent, respectively, in three normal human livers. The livers of Cases 4, 6 and 9 in the present series (Table IV) show percentile distributions which are very close to Thann-

checked and gave the value shown in the table. This is, of course, an unusual finding and it must be clearly borne in mind that it has been observed only in this one case. It will be of considerable interest to see whether further studies will support this finding. It is interesting that the liver in Case 5 presented other peculiarities, i.e., the lipid concentration was the highest of any case in the series but in spite of this the plasma fatty acids were not elevated; the water content of the liver was lower than in any of the other livers; and in spite of the tremendously elevated liver lipid the total weight of the liver was only 1,600 Gm. Pathologically, the liver of this case showed a very advanced degree of monolobular cirrhosis and clinically the patient was an emaciated individual. The data bear out again the observations of Terroine¹² that there is an irreducible minimum of fatty acid in the tissues and apparently this

element consists of phospholipids resembling lecithin and cephalin in composition.

In eleven cases (9, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21) vitamin A and carotene were determined in the plasmas and livers. The methods used have been described

previously.^{13,14} The samples of liver were taken from all lobes, thoroughly hashed and mixed and a 5 Gm. aliquot was saponified under nitrogen; the vitamin A and carotene were extracted in the usual way. Following extraction vitamin A was determined in an

TABLE V
VITAMIN A AND CAROTENE VALUES OF PLASMA AND LIVER

Case No.	Days before Death	Plasma			Liver			
		Vitamin A (mμ %)	Carotene (mg. %)	Liver Weight (Gm.)	Vitamin A (mμ %)	Carotene (mg. %)	Total in Liver	
							Vitamin A (mμ)	Carotene mg.
9	6	8.0	.039	4000	None	0.20	None	8.0
12	6	7.5	.075					
	0	5.0	.063	1340	625.	0.13	8,375	1.7
13	180	18.0	.125					
	0	29.0	.156	3800	2225.	0.33	84,550	12.5
14	41	5.0	.050					
	1	6.0	.086	1450	100.	0.40	1,450	5.8
15	118	10.0	.072					
	85	12.0	.096					
	81	10.0	.108					
	59	10.0	.120					
	3	6.0	.090					
	0	5.0	.066	1100	860.	None	9,460	None
16	24	8.0	.067					
	15	10.0	.060					
	6	7.0	.096					
	0	6.0	.090	5000	42.	0.02	2,100	1.0
17	52	10.0	.144					
	24	10.0	.149					
	15	10.0	.132					
	7	7.2	.108					
	0	5.0	.100	580	3514.	0.21	20,381	1.2
18	77	6.0	.060					
	18	12.0	.120	1240	666.	0.16	8,258	2.0
19	6	12.0	.075	1100	600.	0.17	6,600	1.9
20	50	4.8	0					
	32	2.4	0					
	10	5.0	.012					
	1	2.4	0	1150	None	None	None	None
21	43	11.0	.120					
	15	5.0	.120					
	3	5.3	.120	2200	155.	0.08	4,805	1.7

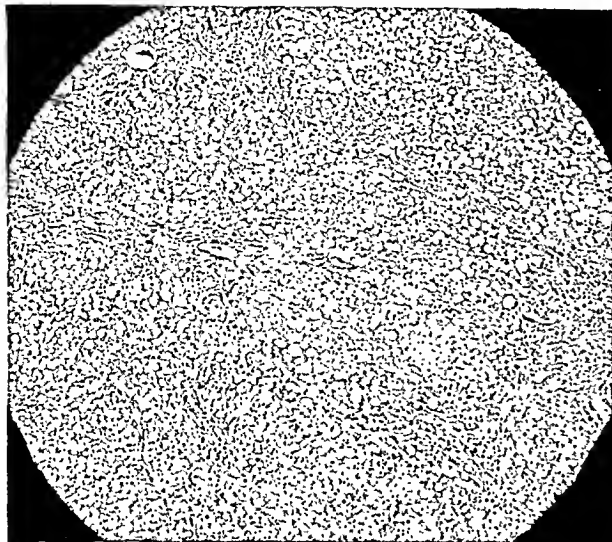


FIG. 4. Case 5. Advanced monolobular cirrhosis and extensive fatty change.† Liver weight, 1,600 Gm.; total lipids, 26 Gm. per cent.

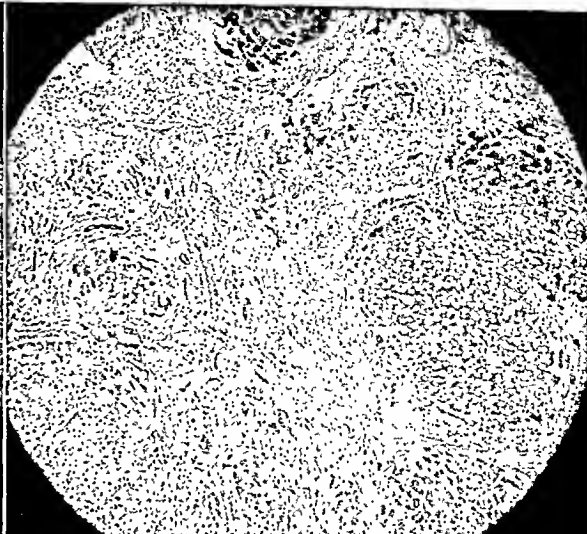


FIG. 5. Case 19. Advanced multilobular cirrhosis. Minimal fatty change. Liver weight, 1,100 Gm.; total lipids, 4.6 Gm. per cent.

Evelyn photoelectric colorimeter which had been standardized with crystalline vitamin A using a 620 m μ filter. This was a change from the method originally used and made it possible to report the values for vitamin A in micrograms. The plasma values for vitamin A were, as was to be expected, well below the normal level.¹³ In a group of twenty normal males plasma values for vitamin A ranged from 48 to 33 micrograms per cent, the average being 38 micrograms per cent. In this group with cirrhosis of the liver the vitamin A levels of the livers ranged from 2.4 to 29 micrograms per cent with an average of 8.4 micrograms per cent. Carotene values averaged .085 mg. per cent with a range from 0 to .156 mg. per cent, the latter being in Case 13 who had diabetes mellitus. These values are also somewhat below the normal range of .085 to .230 mg. per cent. (Table v.)

The pathologic changes in the livers of the patients were so characteristic of the already well described lesions of periportal fibrosis that it would be redundant to publish microphotographs of all the cases. The microphotographs of the microscopic sections of two cases are shown which illustrate the character of the pathologic changes observed. Case 5 (Fig. 4) showed

advanced monolobular cirrhosis of the liver as well as extensive fatty changes. This was the liver in which the total lipids were 26 Gm. per cent although the weight of the liver was only 1,600 Gm. The microphotograph of the microscopic section of Case 19 (Fig. 5) showed advanced multilobular cirrhosis with minimal fatty change. Total liver lipids in this liver were 4.6 Gm. per cent and the weight of the liver was 1,100 Gm.

COMMENT

These observations on lipid fractions in the plasmas and livers of the same patients show that there is no absolute correlation between the amounts of total fatty acids in the plasma and in the liver. As can be seen in the figures, total fatty acids in the plasma may be elevated without a regularly associated increase in the concentration of fatty acids in the liver. The interval of time elapsing between the taking of the blood sample and the liver sample is naturally of considerable interest because of the possible influence of the time interval on the relationship of the lipid fractions. (See Table II.) In cases in which it was possible to do repeated fractionations of plasma lipids (Cases 6, 8, 14, 15, 16 and 20),

the time intervals varied from 254 days to the day of death, thus making it possible to evaluate the consistency of the relationship between plasma and liver lipids over a considerable period. In some of the cases plasma samples analyzed shortly before death showed a definite increase in the ratio of free to total cholesterol, suggesting a diminishing functional capacity of the liver in respect to the esterification of cholesterol. This, however, was not always the case as is shown in Case 6 in which the ratio of free to total cholesterol fell from a peak of 73 per cent on the fifteenth day before death to 46 per cent on the third day before death. Total plasma lipids remained fairly consistent on repeated analyses. In Case 20 in which the original determination had been done 254 days before death, the total lipids rose from 424 mg. per cent to 589 mg. per cent, and the total fatty acids rose from 232 mg. per cent to 428 mg. per cent. The results in the majority of cases suggest that once the liver is severely damaged the alteration in the plasma lipid fractions remains relatively constant. In none of the cases was there any significant clinical improvement during the course of therapy, which consisted of a highly nutritious diet and large doses of vitamin B complex. In some patients in whom clinical improvement and recovery of liver function had occurred the ratio of free to total cholesterol had returned to within normal limits after a considerable period of time.²¹

The discrepancy in the concentration of plasma and liver lipid fractions in patients with chronic liver disease does not seem to us surprising. In the experimental animal more constant results in the relation of plasma and liver lipids may be expected, because liver disturbance is fairly acutely produced and the method of producing liver damage is usually by means of a diet deficient in choline. In the patient with chronic liver disease the situation is entirely different and the process has undoubtedly been going on for years. By the time the patient comes under observation he is severely ill and often in a terminal state.

Furthermore, as is demonstrated in the pathologic examination of the liver, the derangement is advanced and fibrosis and replacement of normal liver tissue is a conspicuous finding. One is therefore making observations at a time when the function of the liver is affected, both because of inadequate amounts of substances such as choline and because of profound destruction of liver tissue. The possibility exists also that when liver lipids are elevated with no change in the concentration of plasma lipids the liver damage has progressed to an extent where the phospholipid turnover in the liver has been blocked. Chaikoff¹⁶ has reported that as a result of experiments in which P^{32} was injected into animals the entrance of fat into the liver and its release from the liver have been linked with the rate of lipid phosphorylation. The effect of choline was to stimulate the rate of phospholipid turnover and this effect was observed despite the fact that the content of total phospholipid in the liver showed no measurable change. It is the opinion of other investigators^{17,18} that the incorporation of phosphate into phospholipid molecules of plasma occurs for the most part in the liver. Fishler¹⁹ studied lipid phosphorylation in the hepatectomized dog. This was done by injecting inorganic P^{32} intravenously immediately after removal of the liver. Almost no phospholipid P^{32} was recovered in the plasma as late as three to six hours after hepatectomy. The amounts of injected P^{32} that had been incorporated into phospholipid of the kidneys and of the whole small intestine were approximately the same as those obtained from these tissues in normal animals. These observations support the idea that the main site of phosphorylation of plasma phospholipid is the liver. Hahn and Hevesy²⁰ found that in perfusion experiments with labelled sodium phosphate in cats that lipemic blood was more effective in the formation of phosphatides in the liver than was normal blood. They interpret this to mean that lipemic blood stimulates phosphatide formation in the liver, and they go on to say that as

lipemic blood is changed into normal blood the excess phosphatides are taken up by the liver until "normal" phosphatide content of the blood is reached. In the patient with cirrhosis of the liver the first stage of the disease is probably that of fatty infiltration and at this point the liver is under considerable stress to maintain a rate of phosphorylation that will keep the plasma lipid fractions normal. Obviously as it fails to do this more and more fat is piled up in the organ and circulation to the liver cells is impaired with consequent necrosis. Eventually the liver is so badly damaged that the patient is in much the same state as the hepatectomized dog and in respect to lipid metabolism this means that phosphorylation is impaired and the plasma lipids may be low and fail to reveal changes in the liver lipids. The nutritional status of the patient and the duration of the symptoms of liver disease may also bear some relation to the disturbances evident in the plasma lipids. For example in Figure 1 the symptoms of liver disease were of short duration in Cases 3, 4, 12 and 16. Cases 3 and 4 were obese and showed no evidence of malnutrition. Case 13 in this group was in a fair nutritional state although the symptoms of liver disease dated back for two years; this patient also had diabetes.

Peters and his collaborators¹⁵ fractionated the plasmas in a group of patients with various types of liver disease and in nine of these patients liver biopsies were done and the liver lipids were also fractionated. The changes in liver lipids of these nine patients (seven had either fatty infiltration of the liver or cirrhosis, one had a carcinoma of the pancreas, and in the remaining patient the liver was normal) showed the same pattern as we have observed. The fatty acids in the liver were above normal limits in three of his patients, and in the plasmas of those patients the range in the serum fatty acids was from 9.5 to 26.2 mEq./L. Obviously in his cases, as in ours, there was no absolute parallelism between the concentration of fatty acids in the serum and in the liver.

The most reliable index to the pathologic

state of the liver is the ratio of free to total cholesterol in the plasma and, as shown in Figures 1 to 3, in all of the patients with cirrhosis this ratio was inverted regardless of the amounts of total cholesterol. Peters et al.¹⁵ observed this same change in their patients with portal cirrhosis. They also reported that the cholesterol fraction was usually low or normal. In the patients in our study the cholesterol fraction was elevated when the other lipid fractions were elevated, with the exception of two cases.

We observed as have Peters et al.¹⁵ that plasma phospholipids in general parallel the total plasma cholesterol in patients with liver disease. In the cases we studied this ratio was quite constant but as the phospholipids rose the proportional rise in total cholesterol was not as great. This relationship was not apparent when the liver phospholipid was plotted against the total cholesterol in the liver.

Neither vitamin A nor carotene levels in either plasmas or livers bore any relationship to the concentration or distribution of the fatty acids. Although the metabolism of these fat-soluble substances is profoundly disturbed in patients with cirrhosis of the liver, the mechanism of this disorder is probably not the same as that which controls the fatty acid disturbance. In only two cases was the total amount of vitamin A in the liver high (Cases 13 and 17). One of these (Case 13) had diabetes mellitus and the plasma levels of both vitamin A and carotene were the highest of any in the series. The carotene concentration in the liver of this patient also was increased. Case 17 received large doses of vitamin A intramuscularly and this undoubtedly affected the vitamin A concentration in the liver.

SUMMARY

The plasma and liver lipids were determined in twenty-one subjects, nineteen of whom had cirrhosis of the liver. All of the subjects were adults and nine were females. Of the nineteen patients with cirrhosis, sixteen had ascites and fifteen were jaundiced. The liver samples were obtained at post-

mortem. The time interval between the blood and liver samples varied from twenty-four hours to 254 days. The values for the various lipid fractions over these periods of time were altered significantly in only one case. None of the patients improved clinically to any significant extent during the period of observation.

The most consistent and outstanding change in the plasmas in all of the patients with cirrhosis of the liver was the alteration of the ratio of free to total cholesterol which was inverted in every instance. Plasma lipids were elevated in seven cases, and in three patients this was associated with a marked increase in the liver lipids. In a total of five cases liver lipids were greatly increased. In twelve patients the only significant change in lipid distribution in the plasma was in the ratio of free to total cholesterol.

The per cent water was determined in the livers of six patients. When lipid fractions were calculated on the basis of the dry weight of the liver, their relation to each other was unchanged.

Partition of the phospholipids was done in four of the livers, and the relative concentrations of lecithin, cephalin and sphingomyelin in three of these cases were very similar to those reported by Thannhauser and showed an average percentile distribution of phospholipids of 63.3, 31.6 and 5.0 per cent, respectively.

Vitamin A and carotene levels were determined in the plasmas and livers of eleven of the cases. Vitamin A levels in plasma were uniformly low and carotene was also below normal levels in most of the cases. In all but two of the livers the vitamin A and carotene levels were below normal values.

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Renal Tubular Excretory Capacity for Penicillin in Health and in Subacute Bacterial Endocarditis*

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IT has been amply shown that penicillin is largely excreted by the kidneys without appreciable destruction in the body¹ and that this process occurs rapidly¹ thus playing an important part in limiting the usefulness of that drug in the treatment of infection.

The belief that penicillin leaves the kidneys not only through glomerular filtration but also by tubular excretion has been substantiated by the work of Rantz and Kirby² on penicillin clearances. These investigators showed that the amount of blood cleared of penicillin by the kidneys per minute compared with that cleared of diodrast, another substance excreted by the renal tubules.³ In addition the clearance values of penicillin are far higher than those of such drugs as inulin which is known to be excreted solely by glomerular filtration. Rammelkamp and Bradley,⁴ who showed that elimination of penicillin is retarded when penicillin and diodrast are given simultaneously, suggested that there existed between these two drugs a competition for the same mechanism of tubular excretion. This has also been shown to be true of paraaminohippuric acid.⁵

It was of practical importance, therefore, to know the maximal tubular excretory capacity (TM_p) of the kidneys for penicillin since doses of the drug surpassing TM_p would be expected to produce relatively more rapid rises in the blood levels of penicillin than amounts under this level.

It is already known that with renal damage penicillin excretion is hindered along with other renal functions and that high and sustained blood levels may follow relatively small doses.⁶ In diseases in which renal damage occurs and which are susceptible to treatment with penicillin renal failure might then paradoxically exert a favorable influence on the direct outcome of the illness. One disease to which these events are applicable is subacute bacterial endocarditis which in most cases has been found highly amenable to penicillin and in which a high percentage of cases has more or less renal damage.⁷

It is of interest then to know of how much importance the renal damage in subacute bacterial endocarditis is in producing higher than usual blood levels of penicillin. Loewe, Rosenblatt and Altire-Werber⁸ found that in a case of a patient with resistant endocarditis receiving large doses of penicillin by continuous intravenous drip the serum levels of penicillin began to rise above the expected levels when a dose of 625,000 units per hour was reached. It was suggested that at this dosage the TM of penicillin had been attained. It has been shown that with lower continuous intravenous dosages the rise in serum penicillin concentration is directly proportional to the increase in dose.² With these points in mind, serum levels, urinary excretion and serum clearances of penicillin in normal individuals and in patients with subacute bacterial endocarditis have been studied.

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METHODS AND MATERIALS

Penicillin Determination. The concentration of penicillin in serum and urine samples was determined by the tube dilution method of Kirby and Rantz,⁹ a modification of the Rammelkamp technic.¹⁰ The blood samples were collected and the serum removed asep-

to fast and to force water by mouth during the procedure. Those patients receiving intramuscular penicillin prior to the test were given their last dose not less than six hours previous to the beginning of these studies.

Urine. Collection of urine specimens began not less than thirty minutes after starting the

TABLE I
CLINICAL DATA ON SUBJECTS STUDIED

Subject	Age	Surface Area (sq. m.)	Diagnosis	Urinary Studies*										Remarks
				Blood Urea (mg. %)	PSP Excretion†		Volume (cc. per 24 hr.)	Specific Gravity	Reaction	Protein (Gm. per 24 hr.)	White and Epithelial Cells (million per 24 hr.)	Red Cells (million per 24 hr.)	Casts (100,000 per 24 hr.)	
					Time min.	Per cent								
P	43	1.56	Subacute bacterial endocarditis	50	81	30	1044	1.014	1.168	24	20	32	No cardiac failure; heart normal size
G	54	1.89	Subacute bacterial endocarditis	62	120	27	2520	1.010	0.762	2	128	2	No cardiac failure; heart normal size
R	43	1.93	Mild hypertension Subacute bacterial endocarditis	25	120	80	1644	1.014	0.000	4	0	0	No evidence of cardiac failure except slight cardiac enlargement
T-test 1	41	1.62	Subacute bacterial endocarditis	35	120	80	504	1.024	Acid	0.036	1	1	0	Moderate cardiac enlargement but no other evidence of failure
T-test 2	Relapsed subacute bacterial endocarditis	..	120	75	432	1.024	Acid	0.032	0	0	0	Heart a little larger, otherwise the same
E	48	1.61	Gumma of the skin	27	120	85	1368	1.019	0.000	9	3	1	Marked secondary infection of gumma Poor cooperation in forcing fluid
C	28	1.86	Healthy	33	120	75	1117	1.016	Acid	0.042	1	0	0	No history of renal disease
B	31	2.00	Healthy	30	120	70	1014	1.017	Acid	0.039	1	0	0	No history of renal disease

Time elapsed between tests 1 and 2, patient T, seventy-nine days.

* Addis count.

† 6 mg. PSP injected intravenously at start of test.

tically. The urine was passed through a Seitz filter. When delays occurred in performing the determinations, the samples were kept in a frozen state in the dry ice refrigerator. Two or more determinations were made on each sample and when results differed they were averaged.

Administration. Crystalline sodium or potassium penicillin was dissolved in 500 cc. of isotonic saline in all but two instances and administered intravenously at as constant a rate as possible. The times of commencement and completion of each dose were recorded. Subjects received only water after the evening meal of the preceding day and were required

intravenous administration of penicillin, with two exceptions: Subject P, dose No. 2, after twenty-five minutes, and Subject T, dose No. 3, after sixteen minutes. Specimens were collected over a timed period of thirty minutes or more except in two instances: Subject T, dose No. 1, twenty-six minutes, and dose No. 3, nineteen minutes.

Blood. Two samples were collected, one at the beginning and one at the end of each urine collection in Subjects B, C, E and T (Dose Nos. 4 and 5). One sample was collected at the midpoint of each urine collection period in Subjects P, C, B and T (Dose Nos. 1, 2 and 3).

Sources of Error. Penicillin determinations in samples of high concentration were at times inaccurate because as the higher levels were reached the difference in penicillin concentration between two consecutive tube readings was large (up to several thousand units). In

nation of the intravenous drip. These periods, however, were never longer than a few minutes.

The rate of flow of the solution was not constant at all times. An attempt was made to administer the penicillin to Patients P, G, R and T (Dosage Nos. 1, 2 and 3) over a pre-

TABLE II
ABSORPTION, EXCRETION AND CLEARANCE OF INTRAVENOUSLY ADMINISTERED PENICILLIN

Sub- ject	Dose No.	Penicillin Administered (units per hr.)	Urine			Serum Penicillin Concentration (units per cc.)	Clearance Serum Cleared of Penicillin (cc. per min.)
			Excretion (cc. per min.)	Penicillin (units per cc.)	Penicillin Excretion (units per min.)		
P	1	40,246	4.80	66	317	2.00	158
	2	500,000	5.50	500	2750	20.00	135
G	1	50,000	7.47	100	747	5.00	149
	2	100,000	7.73	100	773	5.00	155
	3	500,000	5.77	400	2308	20.00	116
R	1	50,000	11.10	50	555	1.00	555
	2	100,000	10.89	100	1089	1.00	1089
	3	546,000	13.66	400	5464	10.00	546
T	1	44,760	11.35	20	227	1.00	227
	2	263,500	9.84	100	984	10.00	98
	3	1,621,000	11.05	500	5525	50.00	111
	4	63,500	8.08	100	808	2.00	404
	5	351,500	6.08	600	3648	15.00	243
E	1	50,000	0.68	1000	680	0.80	850
	2	411,000	0.68	6000	4080	10.00	408
	3	2,050,000	0.55	30000	16500	100.00	165
	4	4,720,000	1.67	40000	66800	300.00	223
C	1	45,780	9.30	59	544	0.50	1088
	2	411,000	4.43	1400	6202	6.38	972
	3	774,180	6.03	1750	10553	12.50	844
	4	1,655,160	5.52	4000	22080	25.00	883
	5	3,318,000	11.49	4500	51700	91.50	565
	6	4,900,000	9.06	6666	60393	150.50	403
B	1	58,200	13.98	31	433	0.76	570
	2	504,000	8.37	666	5570	9.50	586
	3	892,000	9.74	1250	12180	18.75	650
	4	1,790,000	4.84	6666	32120	60.50	533
	5	3,650,000	14.68	2000	29360	91.50	321
	6	4,025,000	1.93	30000	57900	150.00	383

cases in which there seemed to be an obvious discrepancy the samples were reassayed and interpolation dilutions were made between the two penicillin concentrations in question.

Some of the patients had difficulty in voiding and urine collection periods ran past the termi-

determined period thus necessitating occasional acceleration or retardation of the intravenous drip. Subsequent determinations were made at an almost constant speed of delivery with a calibrated Murphy drip, making it possible to administer the solution in the approximate

period desired without changing the rate of flow.

Subjects. Patients P, G, R and T were under treatment for subacute bacterial endocarditis proven by blood culture.

Patient E, with a diagnosis of tertiary syphilis

each dosage in each subject furnished the data for determinations of serum clearances. The rate of urine flow was found to bear no relationship to the per cent of penicillin excreted, and as large a portion of the dose was excreted with a urine flow of 0.68 cc.

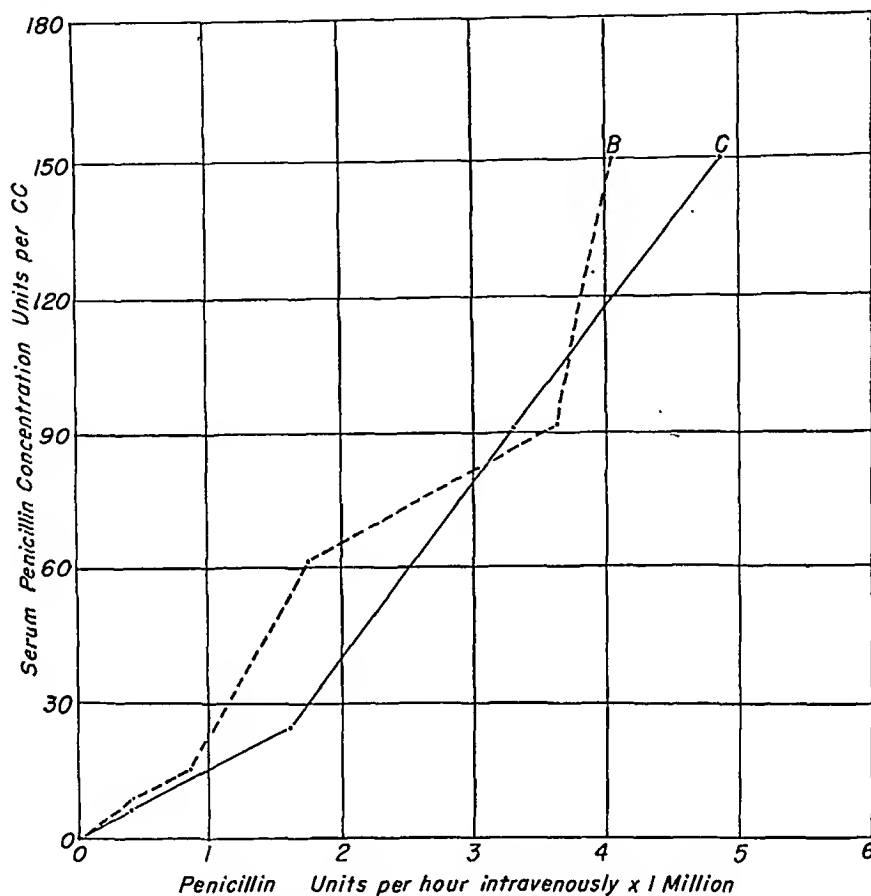


FIG. 1. The relationship of the rate of penicillin administration to serum concentration in healthy people.

of the skin with secondary infection, was chosen as a control but his debilitated condition, age forty-eight, and failure to excrete large quantities of urine probably exclude him from this group.

Patients C and B were normal young men in good health. Patients P and G had clear evidence from their urinary studies and phenol-sulfonphthalein excretion values of renal lesions while patients T and R gave no indication of renal disease. (Table I.)

RESULTS

The rate of penicillin administration by the intravenous route was computed as units per hour. The rate of excretion and serum levels of penicillin (Table II) with

per minute (Subject E, dose No. 1) as with a flow of 9.74 cc. per minute (Subject B, dose No. 3). The per cent of penicillin excreted appeared to depend on renal function rather than on the forcing or withholding of fluids.

Table II shows that there are a number of inconsistencies in the penicillin blood and urine concentrations and resultant clearances, and that the absolute values are not as significant as are the trends. Nevertheless, it is possible to draw some clear cut conclusions from these values.

Serum Concentrations. It has been found¹¹ that with continuous intravenous adminis-

tration a plasma level of 1 unit per cc. results from a dose of approximately 41,000 units per hour, and that this level increases in direct proportion to the increase in dosage. Thus, a dose of 410,000 units per hour produces a level of 10 units per cc.

TABLE III
SERUM PENICILLIN CONCENTRATIONS IN NORMAL HUMANS

Sub- ject	Penicillin		
	Intravenous Dose (units per hr.)	Actual serum Concentration (units per cc.)	Expected Serum Concentration (units per cc.)
C	45,780	0.50	1.09
	411,000	6.38	10.01
	774,000	12.50	18.43
	1,655,160	25.00	40.37
	3,318,000	91.50	80.93
	4,900,000	150.50	119.51
B	58,200	0.76	1.42
	504,000	9.50	12.30
	892,000	18.75	21.50
	1,790,000	60.50	43.70
	3,650,000	91.50	89.02
	4,025,000	150.00	98.05

The two normal controls, C and B (Fig. 1 and Table III) attained serum levels close to the expected values with the lower dosages, but with doses of 4,025,000 units (B) and 4,900,000 units (C) per hour the levels were considerably higher. This indicates that the maximum tubular capacity of the kidneys for penicillin had been reached.

The serum concentrations of penicillin in the other patients varied. (Table II.) Those of Subjects R and T were within a normal range. Those of Subjects P and G were higher, pointing to a reduction in their TM_P . The two large doses received by Subject E produced levels well above the expected values, indicating that his TM_P also was reduced. Figure 2 demonstrates these relationships in both normals and patients.

Clearances. Figure 3 shows the rates of renal clearance of penicillin at various dosage values in healthy and sick human

beings. Assuming that clearance values for penicillin below TM_P are the same as those for diodrast below TM_D , the lower limit of normal should be 561.1 cc. of serum cleared of penicillin per minute (normal males corrected to a surface area of 1.73 square meters).

The clearances were above this figure in the two normals, C and B, with the lower dosages of penicillin. Whether this is due to errors in the dilution technic for penicillin determination or to differences in tubular mass is not known but the consistently higher curve of Subject C probably means that this TM_P was considerably greater than that of B. (Diodrast clearances in healthy males may vary by as much as 271.8 cc. of plasma per minute.)³ Clearances began to drop sharply between dosages of approximately 1,500,000 and 3,500,000 units of penicillin per hour.

Patient R's clearances were also normal and his TM_P was probably not reached since the first and last values were approximately the same. The wide variation in his figures may be attributed to technical error. Subject E's initial clearance, which was similar to those of the normals, dropped below this level with a dosage of only 411,000 units of penicillin intravenously per hour, suggesting that he did have a diminished tubular excretory capacity. Patients P and G whose renal studies were grossly abnormal showed very low clearances, a finding compatible with their relatively high serum penicillin concentrations. Although the renal studies of Patient T were normal, his clearances on two occasions were abnormal. The fact that his serum penicillin concentrations were, for the most part, higher than expected suggests that he did have decreased renal function.

COMMENTS

The data presented above have confirmed previous work showing that penicillin* is excreted by the kidney tubules. For normal males the maximal tubular capacity has

* The penicillin used in this study was generously donated by the Commercial Solvents Corp.

been found to lie between 1,655,160 and 3,650,000 units of penicillin intravenously per hour. Since the serum concentrations attained with dosages of 3,650,000 (B) and 3,318,000 (C) units of penicillin per hour were still approximately the expected levels

dose, it may be concluded that approximately 3,000,000 units of penicillin per hour intravenously, or 50,000 units per minute, is the TM of penicillin. The crystalline penicillin used contained 1,600 units per mg. Therefore, the maximal tubular excre-

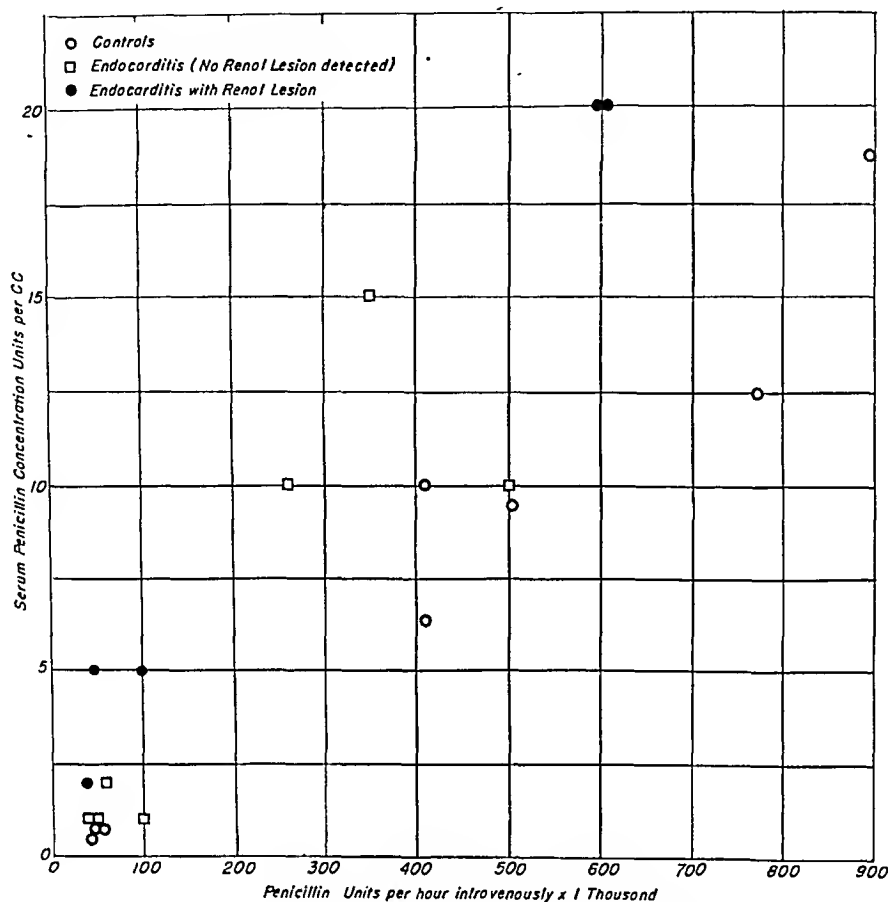


FIG. 2. Serum concentrations of penicillin in sick and healthy people.

with that dosage, it can be assumed that TM_F actually lies much closer to 3,650,000 than to 1,655,160 units of penicillin administered intravenously per hour. After TM is reached tubular excretion can no longer increase by definition and, therefore, any increase in excretion resulting from doses above TM must result from an increase of the drug in the glomerular filtrate. The result would be a relatively precipitous rise in the serum concentration of penicillin. Since this rise did not occur with doses in the neighborhood of 3,500,000 units per hour and since the sharp drop in clearance values occurred somewhere between that dose and the previous lower

tory capacity of normal kidneys for penicillin is approximately 30 mg. per minute, or 1,800 mg. per hour.

The same conclusions may be reached by the calculation of glomerular and tubular excretion of penicillin at each dosage level. Using the data of Table II and the value of 131 cc. per min. per 1.73 square meters of surface area³ as the glomerular filtration rate, in Subject C it was found that the ratio of tubular to glomerular excretion of penicillin for the first four doses lay between 7.8 and 6.0. On the fifth dose it dropped to 4 and on the last dose to 2.9.

In Subject B the ratio varied from 3.5 to 4.3 for the first four doses, dropping to 2.1

and 2.5 on the fifth and sixth doses, respectively. Therefore, on the fifth dose in each patient, while the glomerular filtration of penicillin continued to rise in proportion to the serum concentration, the tubular excretion failed to increase correspondingly as

normal during life was similar to some of the cases mentioned by Christian⁷ who in spite of normal renal sediments were found at autopsy to have fibrinoid glomerular thrombi and renal infarcts. At autopsy patient T's kidneys showed a mild diffuse

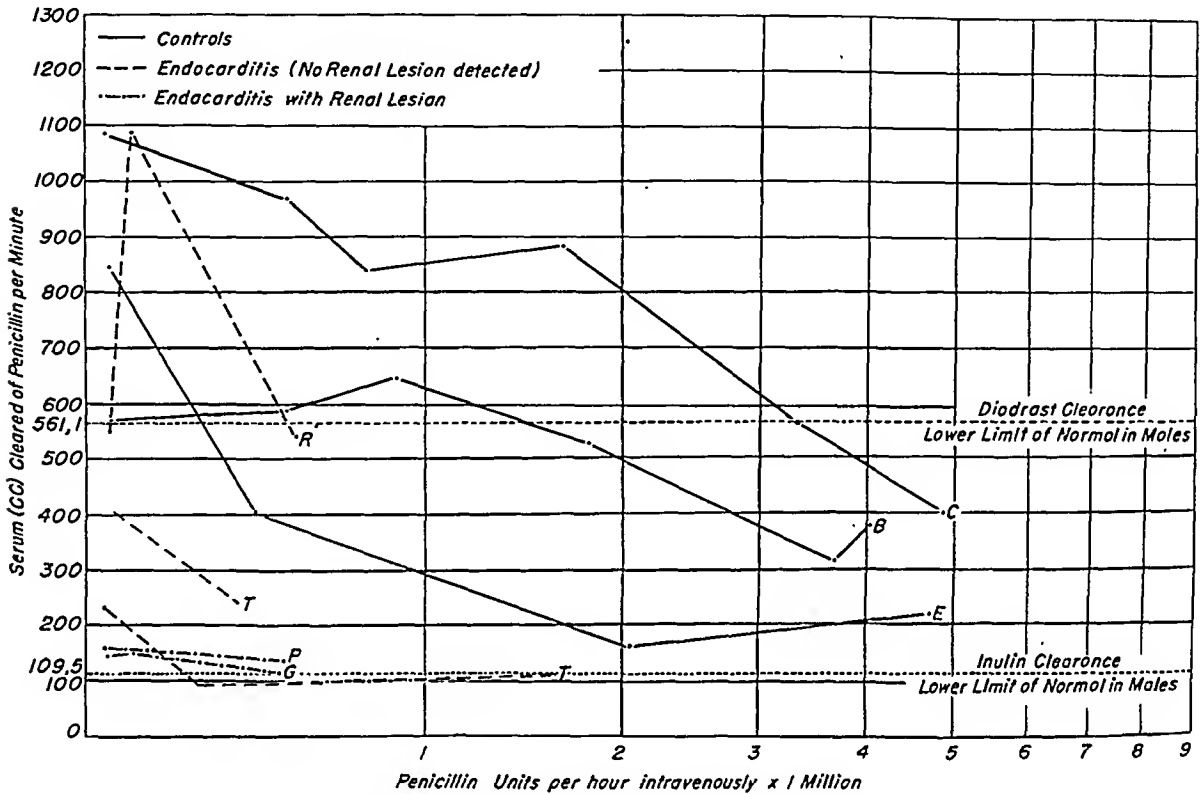


FIG. 3. Penicillin clearances in sick and healthy people.

it had in the lower doses. This again places the TM of penicillin below 3,318,000 and 3,650,000 units of penicillin per hour intravenously and above 1,655,160 and 1,790,000 units per hour.

While the clearances of one patient with subacute bacterial endocarditis were normal, those of three others and of a patient with tertiary syphilis were depressed. In two of these latter patients there were obvious renal lesions. In one, G, whose infection was caused by a highly resistant organism and who was treated with 12,000,000 units of penicillin per day for sixty days, the renal lesion was of distinct benefit since very high levels of penicillin were obtained in his serum.

Patient T whose renal studies were

glomerulitis and a few, small, old renal infarcts. His low clearances were probably the result of these abnormalities plus mild heart failure.

The explanation of lowered clearances in Subject E is not clear unless his age, tertiary syphilis and suppurative skin lesions had combined to decrease his renal function.

The failure of rate of urine flow to affect the per cent of penicillin excreted should discourage attempts to increase the effects of penicillin by dehydration except in cases of susceptible urinary tract infection.

Neither intravenous doses of crystalline penicillin equivalent to 117,000,000 units per day for one hour nor the maintenance of serum levels of 50 to 100 units per cc. in

one subject (G) for sixty days produced toxic effects.

SUMMARY AND CONCLUSIONS

1. Penicillin is excreted by the renal tubules.

2. Clearance values of penicillin are approximately the same as for diodrast.

3. Maximal tubular excretory capacity for penicillin (TM_p) in the normal male is approximately 3,000,000 units (1,800 mg.) per hour, or 50,000 units (30 mg.) per minute.

4. The TM_p and penicillin clearances of certain patients with subacute bacterial endocarditis are decreased and result in supranormal concentration of penicillin in the serum.

5. Rate of urine flow does not affect the rapidity of penicillin excretion.

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Pulmonary Atelectasis in Stuporous States*

A Study of Its Incidence and Mechanism in Sodium Amytal Narcosis

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THE complications of the immobilization which results directly or indirectly from a variety of common illnesses are of general importance. Within recent years attention has deservedly been focused on the frequent and dangerous complications of phlebothrombosis. That restriction of movement has importance in leading to postoperative bronchopneumonia has long been the concern of anesthetists. We believe that a similar or identical mechanism leading to pulmonary complications frequently operates in common medical conditions associated with coma and stupor, and at times, with immobilization in bed without disturbance in consciousness.

Pulmonary atelectasis and related phenomena were observed by the authors during continuous deep sodium amytal narcosis in patients with combat neuroses. In all instances the atelectasis was lobular or segmental and located in one or both lower lung lobes. Usually it was transient. This complication has received scant attention, although bronchopneumonia is frequently found postmortem in patients who succumb to toxic doses of the drug.

Fever is also a common complication of narcosis.¹⁻⁴ No cause for this has been shown, although various suggestions including infection and a central effect of the drug have been made. In most instances the urinary tract, nose, throat, sinuses and ears were found normal. Our experiences confirmed these observations. We noted that

pulmonary atelectasis was always accompanied by fever, although fever was observed in the absence of demonstrable atelectasis. The present study was undertaken to determine the frequency and character of the pulmonary changes during deep sodium amytal narcosis, their mechanism and their relationship to fever and other phenomena in a group of healthy young adults.

METHOD

Approximately 350 patients were studied in this series which was carried out in a U. S. Army hospital in 1943 to 1944. All were young adult males between the ages of twenty and twenty-eight. They were carefully studied prior to treatment and special ear, nose and throat examinations as well as studies of the lungs were made. No patient was narcotized if evidence of infection was present.

Three hundred of these patients were deeply narcotized by sodium amytal in the following manner:⁵ All sodium amytal was administered by mouth and large doses were given only after the patient had been fed. The initial dose for a man weighing 150 pounds was 0.8 Gm. (12 gr.) given at 8 A.M. This was followed two hours later by a second dose of 1.0 Gm. (15 gr.). The patient then slept until about 5 P.M. He was awakened, his mouth, face and hands cleaned and he was taken to the bathroom to void and then was fed. After eating he

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received 1.2 Gm. (18 gr.) of sodium amytal by mouth and was allowed to sleep all night. For the following two days he received 1.4 Gm. (21 gr.) of sodium amytal after breakfast and 1.4 Gm. (21 gr.) after supper. If the required depth of sleep was not obtained by this dosage, additional doses of sodium amytal were given. Often the two main doses had to be either increased or decreased depending upon the weight of the patient and his tolerance to the drug. An average deeply narcotized patient received about 3.0 Gm. (45 gr.) of sodium amytal each day for three days. The patients were fed twice daily, morning and evening, and after each feeding they received their main doses of sodium amytal. They received a minimum of 1,500 cc. of fluid daily in the form of water, fruit juices and milk.

In all patients deep sleep was maintained for forty-eight hours. This necessitated a stay of from sixty to seventy-two hours in the narcosis ward. A patient was considered to be in deep sleep if he did not respond when his blood pressure and temperature were taken, his position changed or when airplanes flew directly overhead. His respirations were shallow and the pupils slightly constricted. He moved sluggishly and only momentarily when the skin was perforated by a pin. He no longer appeared to dream. This depth of sleep was attained twice daily, the middle of the day and the middle of the night. During the morning and evening meals narcosis was relatively light and is referred to as light or drowsy sleep or narcosis. Reference to Figure 7 illustrates a typical three-day period of narcosis. The depth of sleep is indicated at the top of the figure in black. The temperature, pulse, respirations and sodium amytal doses are indicated on the chart.

At the end of three days of narcosis the patients were removed to a recovery ward for one to two days. During the first day of postnarcosis many were still mentally dull,

their muscles hypotonic and their breathing shallow. During the second day all became restless and in spite of ataxia moved around a good deal, usually with assistance. They received sedation only at night.

In fifty deeply narcotized patients detailed x-ray studies were made. The x-ray technic was as follows: The day before narcosis was started a chest x-ray at 6 feet target distance was taken, with the patient standing. The purpose of this x-ray was to rule out a pulmonary pathologic condition prior to treatment. During and after narcosis all x-rays were taken with the patient supine in bed. These films were taken once daily at 1 P.M., the time of day when narcosis was uniformly deepest. Following narcosis they were taken at the same time. Additional films were taken when an unusual rise in temperature occurred or whenever otherwise indicated. These films were taken with a portable army field unit at a 30 inch distance with the central ray directed halfway between the manubrial notch and the xiphoid process. Particular care was taken to avoid the slightest rotation of the patient in order that the chest be well centered. The authors were personally responsible for taking these films. All exposures were made during the height of an average inspiration; care was taken to avoid exposures during irregular respirations. Postnarcosis films were taken during quiet respirations to simulate as nearly as possible the conditions of the narcotized patient. The exposure factors for individual patients were always the same to insure uniformity of radiographs.

The following additional studies were made in deeply narcotized patients: (1) Eight patients were fluoroscoped on several occasions with a portable unit in the narcosis room and tracings of the diaphragmatic excursions were made. (2) Respiratory tracings were obtained during the breathing of air and oxygen with a Sanborn Waterless (type 8 MC) basal metabolism machine in

twelve patients. These were utilized to determine the average tidal air in deeply narcotized patients. (3) Samples of arterial blood were withdrawn under oil from the radial artery of eight patients for comparison of their color before and after the breathing of oxygen. This was to determine if the cyanosis of the mucous membranes and nail beds was accompanied by cyanosis of the arterial blood. (4) White blood counts, differentials and sedimentation rates were determined when indicated and the urine was examined daily during narcosis. The Wintrobe method for determining sedimentation rates was employed and 10 mm. was considered the upper limit of normal. (5) In eight patients daily hematocrit determinations were made to rule out dehydration as a cause of fever.

The fifty remaining patients were more lightly narcotized (receiving 2.0 Gm. (30 gr.) of sodium amytal daily). The incidence of fever was determined in these and compared with the incidence of fever in another series of fifty deeply narcotized patients who received an average of 2.9 Gm. (43½ gr.) of sodium amytal daily.

FINDINGS

General Clinical Observations. The following clinical phenomena were observed in narcotized patients: During the induction of narcosis the respirations were shallow and irregular. Sometimes periods of apnea occurred. As the narcosis deepened the breathing became regular with a rate of 18 to 20 per minute but very shallow. The pupils became moderately constricted still reacting to light. A subsequent dilatation of the pupils heralded deeper and alarming narcosis. Muscle tone gradually lessened with a concomitant loss of reflex activity. Analgesia usually developed to a degree that when blood was withdrawn from the radial artery, the patient would either not move or only make an initial weak attempt

to withdraw his arm. Loud noises did not disturb patients in deep narcosis and they no longer appeared to dream. Examination of the chest during deep narcosis revealed both diaphragms elevated, breath sounds faint but otherwise normal and no râles. To percussion the chest was normal. Respirations became very shallow and entirely diaphragmatic. The systolic blood pressure usually fell to between 80 and 100 mm. of mercury. In deeply narcotized patients the skin, particularly of the extremities, was cool even when some fever was present.

Narcosis of this depth, referred to as deep sleep or deep narcosis, was attained twice in each twenty-four hours, the middle of the day and middle of the night. In the intervals the narcosis lightened and is referred to as light or drowsy sleep or narcosis. During these latter periods (morning and evening) the patients were toileted, fed and medicated. This twice daily fluctuation of narcosis is emphasized at this point as it will be referred to repeatedly in this paper.

The systolic blood pressure at times fell below 80 mm. of mercury during the period of deep narcosis, at which time oxygen was administered for five to ten minutes. This returned the blood pressure to its former or a higher level promptly and it usually remained there. If necessary, oxygen was administered repeatedly. Mild cyanosis of the nail beds and mucous membranes was observed in most patients. Severe cyanosis was not so common and when present it was usually accompanied by falling blood pressure. This complication was also promptly remedied by the breathing of oxygen. A weak pulse, falling blood pressure, severe cyanosis and dilatation of and reduced reactivity of the pupils to light were the danger signals which were vigilantly looked for. The breathing of oxygen and infusion of intravenous 5 per cent glucose in normal saline constituted the only emergency therapy that was ever necessary for these

complications. An occasional patient was bothered by an excess of mucus. This necessitated the frequent use of oral and pharyngeal suction. Fevers appeared to be more common in these patients but an excess of mucus was by no means the cause of fever in all subjects.

TABLE I
INCIDENCE OF FEVER IN LIGHTLY AND DEEPLY NARCOTIZED PATIENTS

No. Cases	Average Daily Sodium Amytal Intake	Axillary Temperatures Above 99°	Axillary Temperatures Above 101°
50	2.0 grams (30 grains)	24%	6%
50	2.9 grams (43½ grains)	46%	20%

Relation of Body Temperature to Narcosis. Variations in body temperature were observed in most narcotized patients. (All temperatures were taken in the axilla. This temperature was 0.6 to 1.0 degrees lower than mouth temperature in narcotized patients.) During the induction and the first four to eight hours of deep narcosis the body temperature usually fell 1 to 2 degrees. On the second and third days the average temperature rose above the first day level and was usually highest when narcosis was deep. Thus, there was usually a twice daily temperature rise, the high points occurring during the mid-day and midnight. Although an elevated temperature was occasionally recorded on the first day of narcosis, this was unusual. It almost always occurred during the second twelve hours and followed an initial fall in temperature.

A further relationship of fever to the depth of narcosis is shown by the following observations of one hundred patients. (Table 1.) In a group of fifty consecutive patients who received an average daily dose of 2.0 Gm. (30 gr.) of sodium amytal, 24 per cent developed an axillary temperature of 99°F.

or more on one or more occasions and 6 per cent of them had fevers of 101°F., or above by axilla. A second group of fifty consecutive patients received a larger average dose of sodium amytal (2.9 Gm. daily; 43½ gr.) and their narcosis was accordingly deeper. Forty-six per cent of these developed an axillary temperature of 99°F. or more and in 20 per cent the temperature rose to 101°F. or more. Thus, an increase in the average sodium amytal intake from 2.0 to 2.9 Gm. more than doubled the incidence of fevers.

The foregoing findings appear to confirm the observation that single large doses of sodium amytal cause a definite lowering of the body temperature.⁶ With continued narcosis, however, new factors are introduced which cause the temperature to rise in proportion to the degree of narcosis.

Observations on Respirations and Oxygenation of the Arterial Blood. The twice daily temperature and narcosis fluctuations were accompanied by concomitant fluctuations in the tidal air, movements of the diaphragm and oxygenation of the arterial blood. The tidal air in deeply narcotized patients averaged 150 to 300 cc. when breathing oxygen. This is a considerable reduction from a normal of about 550 to 750 cc. for young adult males in good physical condition.* During light narcosis (at or about meal time) it was obvious that respirations had increased in depth but still were shallow. Satisfactory measurements of tidal air could not be obtained, however, because the patients were not cooperative in this state. The rates of respiration were altered very little by narcosis, remaining at or about 18 to 20 per minute. Irregular breathing was common and most marked during the change from light to deep or deep to light narcosis. Short periods of apnea or of slowed-down breathing appeared during these

* Personal communication from Dr. Mandel E. Cohen: Under basal conditions and breathing oxygen the tidal air of normal young men averaged 743 cc. and for others with neurocirculatory asthenia, 553 cc.

TABLE II*

Case	Day	Temperature °F.			Respirations		Sodium Amytal Gm./Day	Elevation of Diaphragm		"Shingling"		Lung Changes	
		Average	High	Low	Average	High		Right	Left	Right	Left	Right	Left
1 F. P.	1	97.1	98.0	96.4	18-20	22	2.6	++++	++++	+	+	+	+
	2	97.4	98.0	96.4	18-22	24	3.6	++++	++++	+	+	+	+
	3	97.4	98.0	96.6	18-22	25	4.0	++++	++++	+	+	+	+
	4	++++	++++	+	+	+	+
	5	++++ ₀	++++ ₀	0	0	0	0
2 A. D. A.	1	97.4	98.4	97.0	16-20	21	2.0	+++	+++	+	+	+	+
	2	98.1	98.6	97.0	18-20	21	1.8	++	++	+	+	+	+
	3	97.0†	++	+	+	+	+	0
3 K. I. N.	1	97.0	97.2	97.0	17-20	21	3.8	++++	++++	+	+	+	+
	2	97.6	98.2	97.0	18-22	25	5.0	++++	++++	+	+	+	+
	3	98.0	98.6	97.6	18-20	21	5.2	++++	++++	+	+	+	+
	4	97.6†	++	+	0	0	0	0
	5	0	0	0	0	0	0
4 D. R. A.	1	96.9	97.2	96.4	18-20	20	2.2	++	++	±	±	+	+
	2	98.0	98.4	97.6	18-20	21	1.0	++	++	±	±	±	±
	3	98.0	98.8	97.0	18-20	20	1.0	++	++	±	±	±	±
	4	98.0†	+	+	0	0	0	0
5 B. U. R.	1	96.8	98.0	96.2	18-20	20	3.6	++++	++++	+	+	+	+
	2	98.4	99.4	98.0	18-20	23	3.0	++++	++++	+	+	+	+
	3	97.0†	++++	++++	+	+	+	+
	4	+	+	0	0	0	0
6 K. O. S.	1	97.7	98.2	97.0	18-20	21	3.2	+++	+++	+	+	+	+
	2	98.7	99.2	98.0	18-20	20	2.8	+++	+++	+	+	+	+
	3	98.6	100.0	98.0	18-20	21	2.8	+++	+++	+	+	+	+
	4	++++ ₀	++++ ₀	0	0	0	0
7 G. A. R.	1	97.3	98.0	96.0	18-20	22	3.2	++++	++++	+	+	+	+
	2	98.1	98.8	97.4	18-20	23	2.8	++++	++++	+	+	+	+
	3	97.9	98.4	97.0	18-20	21	2.8	++++	++++	+	+	+	+
8 R. E. F.	1	97.8	99.2	96.6	18-20	22	3.4	+++	+++	+	+	+	+
	2	98.7	99.8	98.0	18-20	20	3.2	+++	+++	+	+	+	+
	3	97.8	99.0	97.0	18-20	20	2.4	+++	+++	+	+	+	+
	4	96.0†	+++	+++	0	0	0	0
9 M. U. S.	1	98.0	98.6	97.4	18-20	20	3.4	++++	++++	+	+	+	+
	2	98.5	99.4	98.0	18-22	22	2.8	++++	++++	+	+	+	+
	3	98.4	98.8	98.0	18-20	20	...	++++	++++	+	+	+	+
10 P. I. N.	1	97.6	98.4	97.2	18-22	22	3.0	+++	+++	+	+	+	+
	2	98.1	99.2	97.0	18-22	24	1.4	+++	+++	+	+	+	+
	3	97.5	98.0	97.2	18-20	22	2.8	++	++	0	0	0	0
	3A	+++	+++	+	+	+	+
	4	97.6	98.0	97.2	18-20	20	4.2	+++	+++	+	+	+	+
	5	98.1	99.4	97.0	18-22	22	2.8	+++	+++	+	+	+	+
11 P. H. O.	1	97.7	98.0	97.4	18-20	21	3.2	+++	+++	+	+	+	+
	2	97.9	98.6	97.6	20-22	26	3.4	+++	+++	+	+	+	+
	3	98.2	98.8	98.0	20	20	2.4	+++	+++	+	+	+	+
	4	98.0†	++	++	+	+	+	+
12 D. A. L.	1	97.3	98.0	96.4	18-20	20	3.0	+++	+++	+	+	+	+
	2	96.9	97.2	96.2	18-20	21	1.6	+++	+++	+	+	+	+
	3	97.9	98.8	97.4	18-20	20	2.0	+++	+++	+	+	+	+
	4	98.0†	++++ ₀	++++ ₀	0	0	0	0
13 W. S.	1	96.8	97.4	96.2	18-20	21	3.0	++++	+++	+	+	+	+
	2	97.5	98.6	96.6	18-21	24	3.0	++++	+++	+	+	+	+
	3	97.2	97.6	97.0	18-20	21	3.8	+++	+++	+	+	+	+
	4	+++	+	0	0	+	0
14 V. A. N.	1	97.8	97.8	97.6	18-20	22	3.8	++++	++++	+	+	+	+
	2	98.1	98.6	97.6	18-22	24	4.0	++++	++++	+	+	+	+
	3	97.6	98.2	97.2	++++	++++	+	+	+	+
	4	++++	++++	+	+	+	+
15 S. T. A.	1	98.0	99.0	96.2	16-20	20	3.0	++++	++++	+	+	+	+
	2	98.1	99.2	98.0	18-20	20	3.2	++++	++++	+	+	+	+
	3	97.9	99.4	96.4	18-20	20	3.4	+++	+++	+	+	+	+
	4	97.2†	++++ ₀	++++ ₀	0	0	0	0
16 M. A. L.	1	97.7	98.6	97.0	18-20	21	3.2	+++	+++	+	+	+	+
	2	98.2	99.0	97.6	18-22	22	2.8	+++	+++	+	+	+	+
	3	98.8	99.2	98.0	18-22	22	3.4	+++	+++	+	+	+	+
	4	99.0†	+++	+++	+	+	+	+
	5	97.6†	++	+	0	+	0	+
17 G. R.	1	97.4	98.2	96.6	18-20	20	3.0	+++	+++	±	±	+	+
	2	98.7	99.6	98.0	18-21	21	3.2	+++	++	±	±	+	+
	3	98.0	99.8	96.0	18-20	20	1.2	++++ ₀	++	0	0	0	+
	4	96.0†	0	+	0	0	0	+

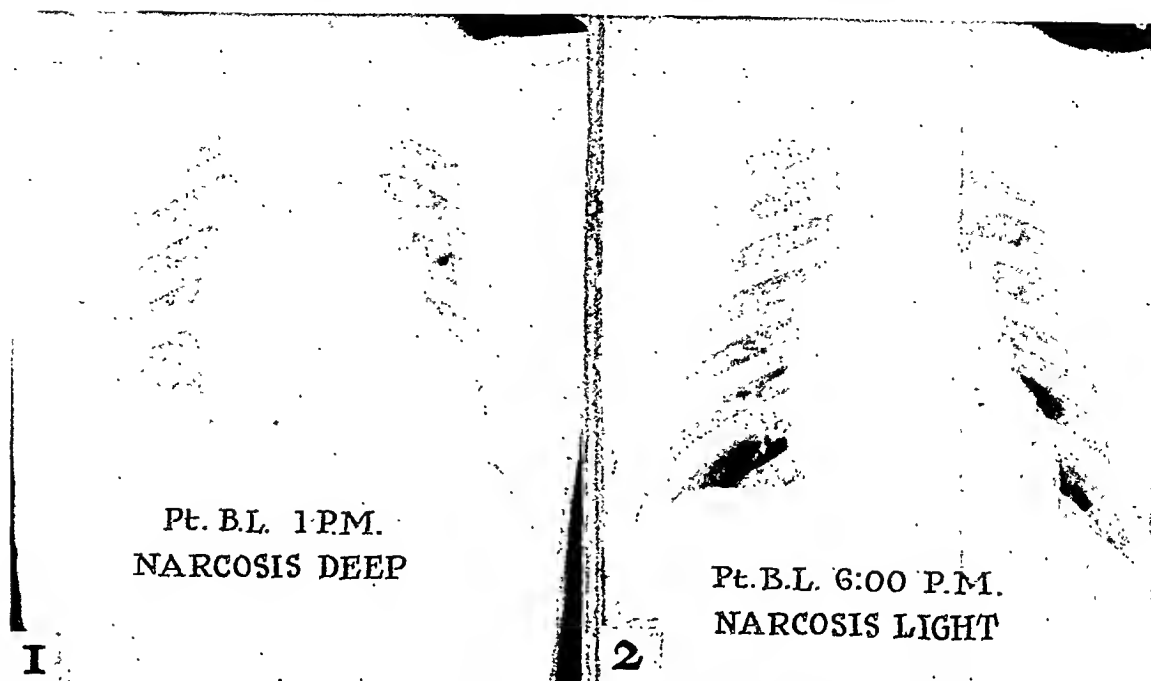
TABLE II.—(Continued)

Case	Day	Temperature °F.			Respirations		Sodium Amytal Gm./Day	Elevation of Diaphragm		"Shingling"		Lung Changes		
		Average	High	Low	Average	High		Right	Left	Right	Left	Right	Left	
18 S. C. H.	1	97.5	98.8	96.2	18-20	21	3.0	++++	+++	+	+	++	+	
	2	98.6	99.4	97.4	18-22	28	3.2	++++	++++	+	+	++	+	
	3	98.9	100.2	97.6	18-20	20	...	++++	++++	+	+	++	+	
	4	97.0†	++	+	+	+	0	0	
	5	+	+	+	+	0	0	
19 F. E.	1	97.6	98.8	96.6	18-20	21	2.2	++++	++++	++	++	++	+	
	2	99.1	101.0	98.4	20	21	1.0	Polymorphonuclears 82% Sed. rate 9 mm.
	3	98.2†	+	+	0	0	0	0	
20 A. C.	1	97.1	97.6	96.6	18-20	20	5.4	++++	++++	+	+	++	+	
	2	99.1	100.0	98.2	18-20	22	4.0	++++	++++	+	+	+	+	WBC 6,250 Sed. rate 9 mm.
	2A	++++	++++	+	+	+	+	
	3	99.6	100.0	98.6	18-20	20	4.2	++++	++++	+	+	+	+	
21 R. O. N.	1	97.3	98.2	97.0	18-20	22	3.6	++	++++	+	++	+	++	
	2	98.7	100.0	98.0	18-20	20	2.4	+++	++++	+	++	+	++	WBC 10,450; Polymorphonuclears 64%; Sed. rate 8 mm.
	2A	+++	++++	+	++	+	+	
22 D. U. K.	1	98.0	100.8	96.0	18-24	26	2.6	+++	++	+	+	++	+	
	2	99.4	100.6	98.0	20-26	28	1.6	+++	++	+	+	++	+	
	3	98.0	98.8	97.0	18-20	20	1.4	+++	+++	+	+	++	+	
	4	98.0†	+++	++	+	+	++	+	
	5	+	0	0	0	+	0	WBC 9,600; polymorphonuclears 72%; sed. rate 6 mm.
23 B. E. R.	1	97.8	100.4	97.0	18-20	24	3.2	++++	++++	±	±	+	+	
	1A	++++	++++	±	±	+	++	
	2	98.0	99.6	96.2	18-20	20	3.0	++++	++++	±	±	++	++	
	3	99.1	99.8	98.0	18-20	23	2.0	++++	++++	±	±	++	++	
	4	98.8†	++++	+	0	0	0	0	WBC 8,250; polymorphonuclears 34% sed. rate 9 mm.
24 M. A. U.	1	97.5	98.8	97.0	18-20	21	3.0	++++	++++	+	+	+	+	
	2	98.1	99.0	97.0	18-22	22	3.2	++++	++++	+	+	+	+	
	3	100.5	102.4	99.4	18-22	36	...	++++	++++	+	+	+	+	WBC 12,000; polymorphonuclears 71%
	3A	++++	+	+	+	+	++	
	4	98.2†	++++	++	+	+	0	++	
25 N. O. T.	1	97.5	99.2	96.6	18-22	24	3.0	++++	++++	+	+	++	+	
	2	99.1	100.4	98.0	18-22	24	3.2	++++	++++	+	+	++	+	
	3	98.4	99.6	97.8	18-20	21	2.8	++++	++++	+	+	++	+	
	4	101.0†	++++	++++	+	+	++	+	
	4A	102.0**	++++	++++	+	+	++	+	WBC 16,000
26 L. E. E.	1	97.6	98.8	96.4	18-20	21	3.0	+++	+++	+	+	+	+	
	2	99.1	100.6	97.2	18-25	32	2.0	+++	+++	+	+	++	++	
	3	97.4	98.2	97.0	18-20	21	3.4	+++	+++	+	+	++	++	
	3A	+++	+++	+	+	++	++	
	4	97.8	98.0	97.4	18-20	22	5.0	+++	+++	+	+	++	++	
	5	98.0	98.8	97.6	18-20	23	2.8	+++	+++	+	+	++	++	
	6	97.4†	+++	+++	+	+	+	+	
	7	97.0†	+++	+++	±	±	+	+	
27 R. A. V.	1	97.3	98.6	97.0	18-24	30	2.4	+++	+++	+	+	+++	+	
	2	99.4	101.4	97.8	20-30	37	2.4	+++	+++	+	+	+++	+	
	3	98.0	98.8	97.4	20-30	33	2.8	+++	+++	0	0	+++	+	
	4	97.6†	+	0	0	0	+++	+	
	5	0	0	0	0	++	0	
28 G. H.	1	97.4	97.4	97.4	18-20	21	3.0	+++	++	+	+	+	+	
	2	98.6	99.6	97.4	18-21	21	2.8	+++	++	+	+	+	+	
	3	100.6	103.0	98.0	18-28	29	1.4	+++	++	+	+	++	+	
	3A	+++	++	+	+	++	+	WBC 10,800; polymorphonuclears 74%; sed. rate 16 mm.
	4	98.0†	++	++	+	+	++	+	

* Contains the essential data on each of the twenty-eight carefully studied patients. All temperatures were taken in the axilla. With reference to elevation of the diaphragm, "+" indicates a rib or interspace, "++" a rib plus an interspace, etc. "Shingling" signifies a collapse of the chest cage; "+" indicates marked narrowing of the interspaces and "++" indicates an actual overlapping of the ribs. In the column lung changes "+" indicates generalized decreased aeration, "++" indicates small focal densities and "+++ moderately large focal densities. (Fig. 16.) In the column labeled remarks, white blood counts and sedimentation rates are recorded. In the temperature and respiration columns, "average" indicates actual averages for twenty-four hours, "high" indicates the single high reading and "low" indicates the single low reading. The total dose of sodium amytal per day is listed in grams.

† Single temperature, 10 A. M.

** Temperature dropped to 98.6°F. by mouth in four hours.



FIGS. 1 AND 2. Figures 1 and 2 are x-rays of the same patient. Figure 1 illustrates the decreased aeration of the lungs, collapsed chest and elevated diaphragm which accompanied deep narcosis. Figure 2 was taken five hours later when the narcosis was lighter and the patient could be fed. Note the increased aeration of the lungs, depression of the diaphragm and widening of the rib interspaces.

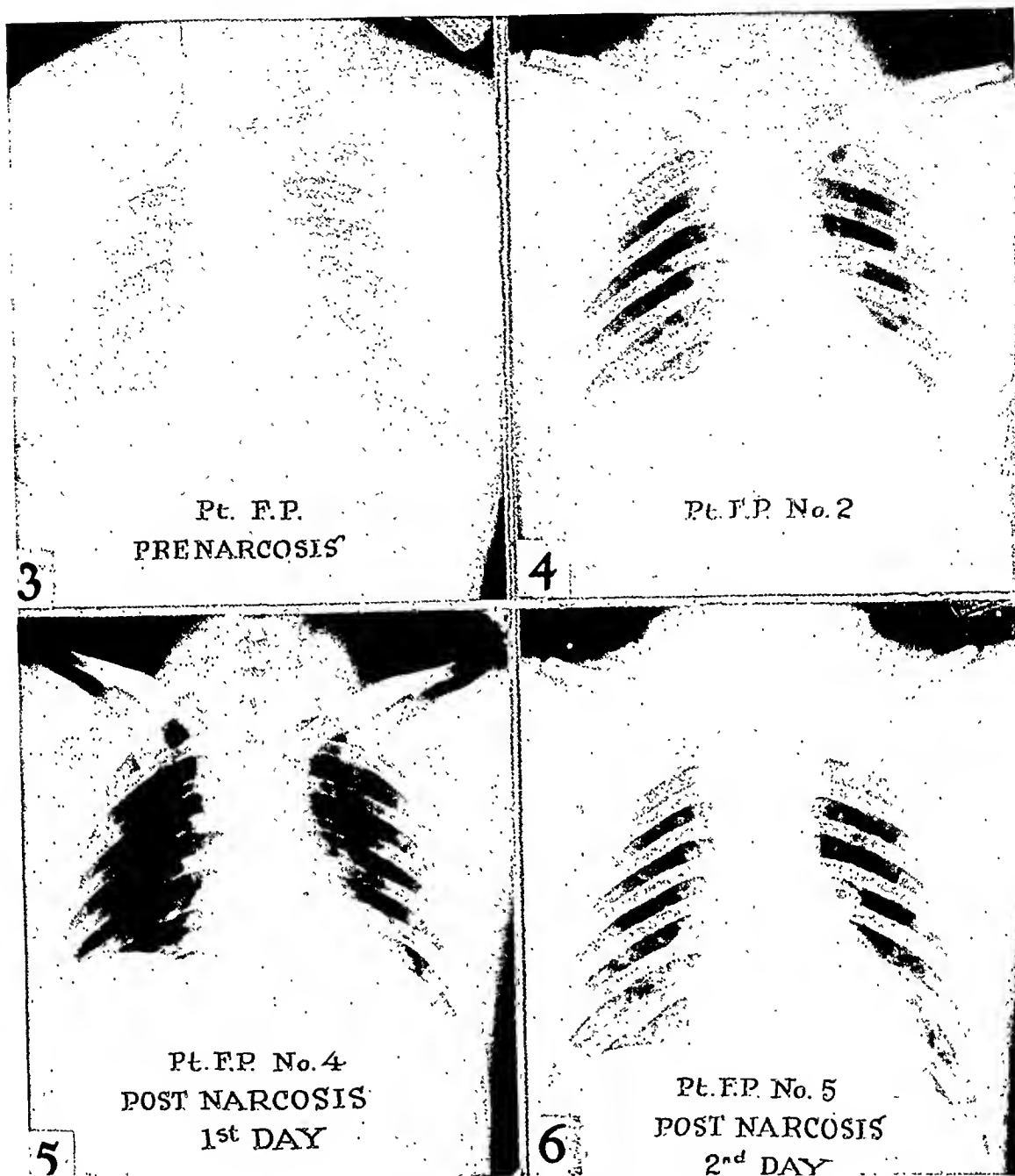
transition periods. During deep narcosis respirations were usually regular.

Moderate rises in temperature (100 to 101°F.) failed to alter either the rate or character of respirations. Higher temperatures, however, were accompanied by significant increases in the respiratory rate and by restlessness. (Table II; cases 22, 26, 27 and 28.) In these patients focal as well as general pulmonary changes were present.

The diaphragms became progressively more elevated and the chest more collapsed as the narcosis deepened. This was accompanied by a corresponding decrease in aeration of both lungs. Figures 1 and 2 illustrate these changes in one patient during deep and light narcosis. These two films were taken five hours apart. Diaphragmatic excursions were also decreased during narcosis. In deeply narcotized patients the excursions of the diaphragm were observed by fluoroscopy to vary between 0.5 and 2.0 cm. and averaged 1.0 cm. This constitutes a marked reduction from a normal of about

3.0 cm. in the average supine young male during quiet respirations.

Cyanosis of the finger nails and mucous membranes was observed in nearly every deeply narcotized patient. This was occasionally severe. In all instances the breathing of oxygen restored these structures to a normal color. It is of some interest that an increase in the depth of respirations, to be discussed later, occurred after the cyanosis had disappeared, suggesting that the increased depth of respirations resulted from, rather than caused, the improved oxygenation of the blood. In eight cyanotic patients arterial blood, drawn under oil from the radial artery, was tinted slightly blue. A second sample of arterial blood obtained in the same way from the same artery by a separate puncture showed that this cyanosis of arterial blood disappeared after oxygen had been assimilated for five to ten minutes. Cyanosis of the mucosa and nail beds had also disappeared.



FIGS. 3 to 6. A series of x-rays of one patient. Figure 3 was taken the day prior to narcosis and is normal. Figure 4 was taken on the second day of narcosis and shows a high diaphragm, slightly collapsed chest and slightly decreased aeration of the lungs. Figure 5 was taken one day after the end of narcosis and shows little change from Figure 4. In Figure 6 greatly increased aeration of the lungs is evident.

Serial X-ray Studies of the Lungs during Narcosis. Fifty patients were studied by daily x-rays taken at mid-day when narcosis was deepest. In twenty-eight patients these studies were complete and technically satisfactory in all respects and are summarized in Table II. In this table the cases

are arranged in order of increasing severity of their pulmonary changes. The first ten cases in this table exhibited only the basic changes characteristic of deep narcosis alluded to before. These are (1) symmetrical elevation of the diaphragms; (2) collapse of the chest cage and (3) decreased aeration

of the lungs. By collapse of the chest is meant a narrowing of the rib interspaces and an increasing slope of the ribs such as one sees in the expiratory phase of respiration. It has already been shown that these basic changes vary with the depth of nar-

postnarcosis day many patients were still quite drowsy and had failed to reexpand their lungs.

A typical representative temperature, pulse and respiration chart for the ten patients showing only these basic lung changes

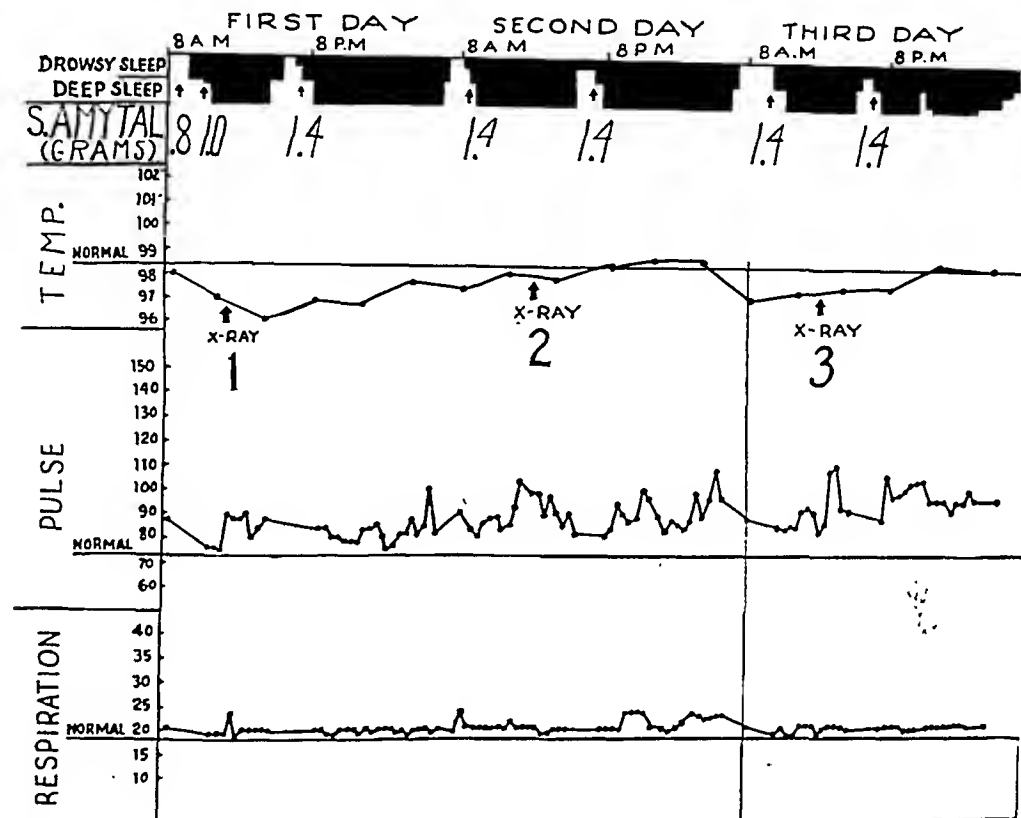
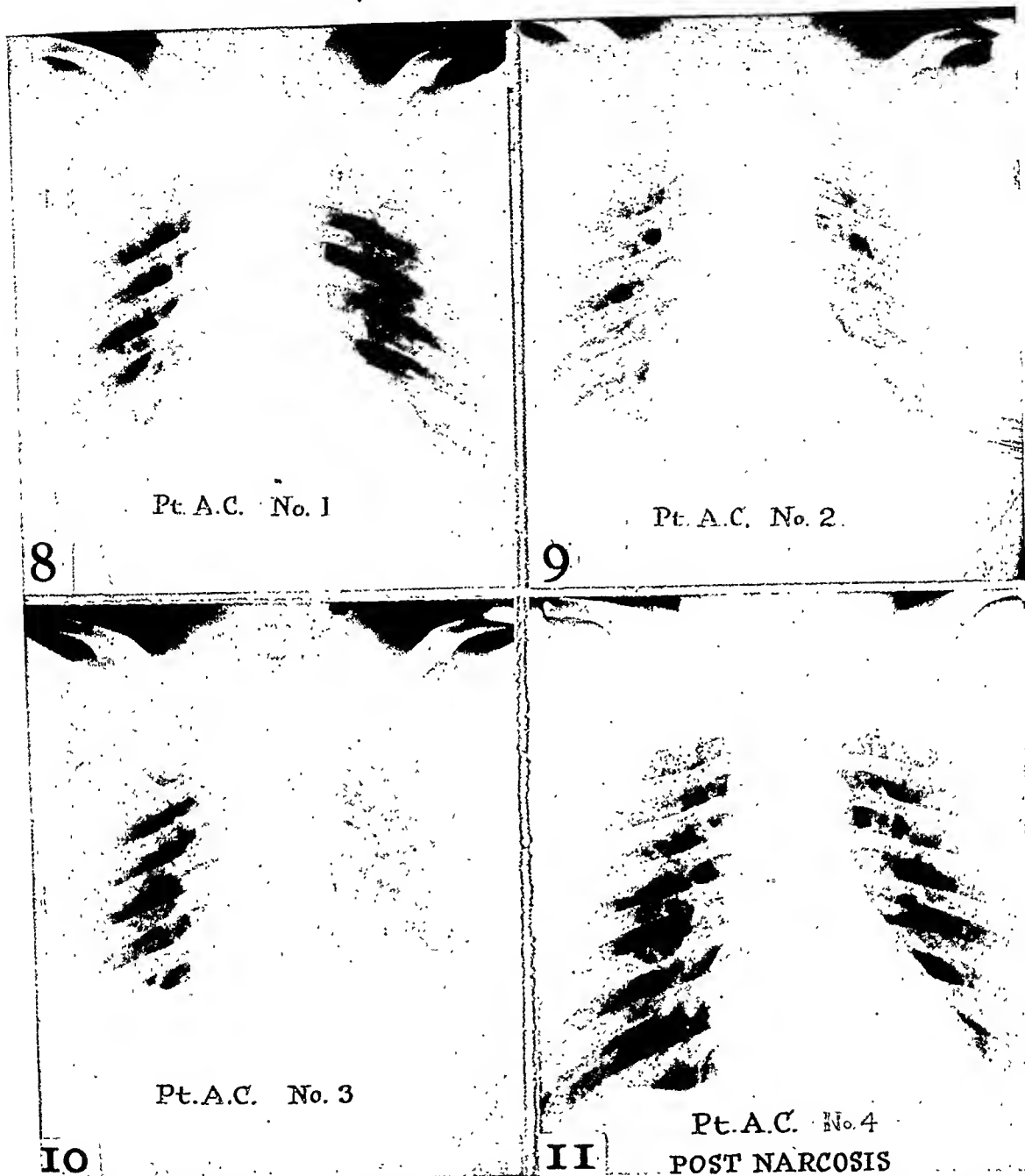


FIG. 7. A typical temperature chart for one of the patients showing only decreased pulmonary aeration. Note the initial drop in temperature. On the second and third days the general level of body temperature is much higher. The arrows indicate when the x-rays were taken.

cosis. Figures 3, 4, 5 and 6 show a representative series of x-rays from one of these patients. The prenarcosis film is normal. (Fig. 3.) Figure 4 is characteristic of the narcosis period and was taken on the second day of narcosis. The diaphragms are elevated bilaterally to just below the third rib on the right and the top of the fourth rib on the left anteriorly. The chest cage is collapsed. The lung fields are poorly aerated but otherwise not remarkable. On the first day postnarcosis (Fig. 5) there is only a slight increase in the aeration of the lungs. On the second postnarcosis day (Fig. 6) the chest is normally aerated. On the first

is shown in Figure 7. Note the initial drop in temperature on the first day followed by higher temperatures on the second and third days. It can be seen in Table II that most of the cases in this group had an elevated body temperature at some time during narcosis. The degree of this elevation was significant in several patients and was highest during deep narcosis. Respiratory changes did not accompany fever in these patients.

The remaining eighteen patients presented further pulmonary changes consisting of (1) asymmetrical elevation of the diaphragm, (2) patchy, irregular densities in the lung fields and (3) minimal changes



FIGS. 8 to 11. A series of x-rays of one patient. In Figure 8 note the high diaphragm, especially on the right, and haziness at the right lung base. This was taken on the first day of narcosis. Figure 9 shows the lungs on the second day of narcosis. There is considerable clearing at the right base. On the following day (Fig. 10) there is haziness at the left base. In Figure 11, which was taken one day postnarcosis, there is marked clearing of both bases. There is still some cloudiness at the left base and slight elevation of the left diaphragm.

in the symmetry of the chest cage. This latter observation was very difficult to evaluate and is probably of the least practical importance because of the difficulty in positioning the patient for x-ray studies; the slightest rotation of the patient produces an asymmetry of the chest on x-ray films.

In fourteen of these patients the pulmonary changes disappeared or markedly diminished in a few to twenty-four hours. Sometimes patches of atelectasis cleared in one lung only to reappear later in the other. Sometimes the densities were so minimal that their nature could be interpreted only

by comparing films taken on successive days. Figures 8, 9, 10 and 11 illustrate these findings. Figure 8 shows the chest during the first day of narcosis. Note the unusual elevation of the right leaf of the diaphragm and the cloudy irregular density at the right

preceding ten patients is one of degree only and no grouping of the cases on the basis of temperature alone is possible. A significant increase in the respiratory rate during atelectasis was noted in only one patient in this group. (Table II, case 22.)

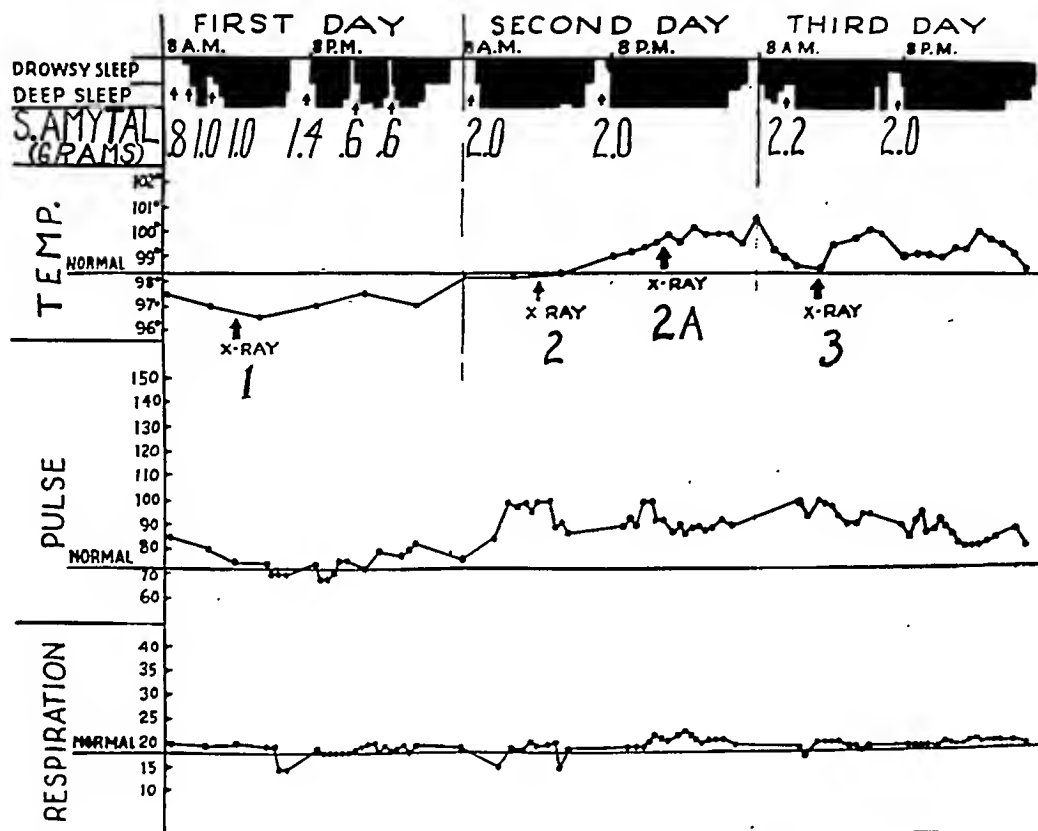


FIG. 12. Temperature chart of the patient illustrated in Figures 8 to 11. The arrows indicate the time that x-rays were taken.

base. Figure 9 is on the second day of narcosis. Note that the right diaphragm has come down and the right base is clear. Figure 10 is on the third day of narcosis and shows haziness throughout the left lung field with definite narrowing of the rib interspaces. Figure 11 is one day postnarcosis. The right lung field is clear, the left diaphragm is still slightly high and the aeration of the lung base although improved is not normal.

The temperature chart for this patient is shown in Figure 12. The low temperature of the first twelve hours is followed by its progressive elevation. The difference between the temperature in these and the

In the remaining four patients the pulmonary changes were more marked and the fever was higher. In two patients the atelectasis disappeared in forty-eight hours and in the remaining two it persisted for four and six days after narcosis. During the bouts of atelectasis three of these patients had significant increases in the respiratory rates and were very restless. Figures 13, 14, 15, 16, 17 and 18 are a series of x-rays from one of these patients. The prenarcosis film (not illustrated) was normal. Figure 13 taken on the first day of narcosis shows no gross change. The lung fields are well aerated. Figure 14, second day of narcosis, shows an elevated right diaphragm with the lung fields less



FIGS. 13 TO 18. A series of x-rays of one patient. Figure 13 was taken on the second day of narcosis. Note the elevated right diaphragm and beginning cloudiness extending out from the right hilus. Figure 15 was taken the third day of narcosis. The right diaphragm is still high and the density in the right lower lung field has increased. In Figure 16, taken later on the same day as Figure 15 (Fig. 19), further cloudiness in the area of the right middle lobe is evident. Also the diaphragm is elevated on the left and the left lower lung lobe is cloudy. There is some clearing in both lungs in Figure 17 taken one day after termination of narcosis. In Figure 18, taken on the second day postnarcosis, both lungs are clear and the diaphragm is in normal position.

well aerated than on the first day. Figure 15, taken on the third day, shows bilaterally diminished aeration, persisting elevation of the right diaphragm and a cloudy density in the right lower lung field. Figure 16, taken the evening of the third day of

eral temperature level was higher in this group of four patients than in either of the two preceding groups. Also, the respiratory rates of three of the patients increased significantly during the atelectasis. (Figure 19, table II, cases 26, 27 and 28.)

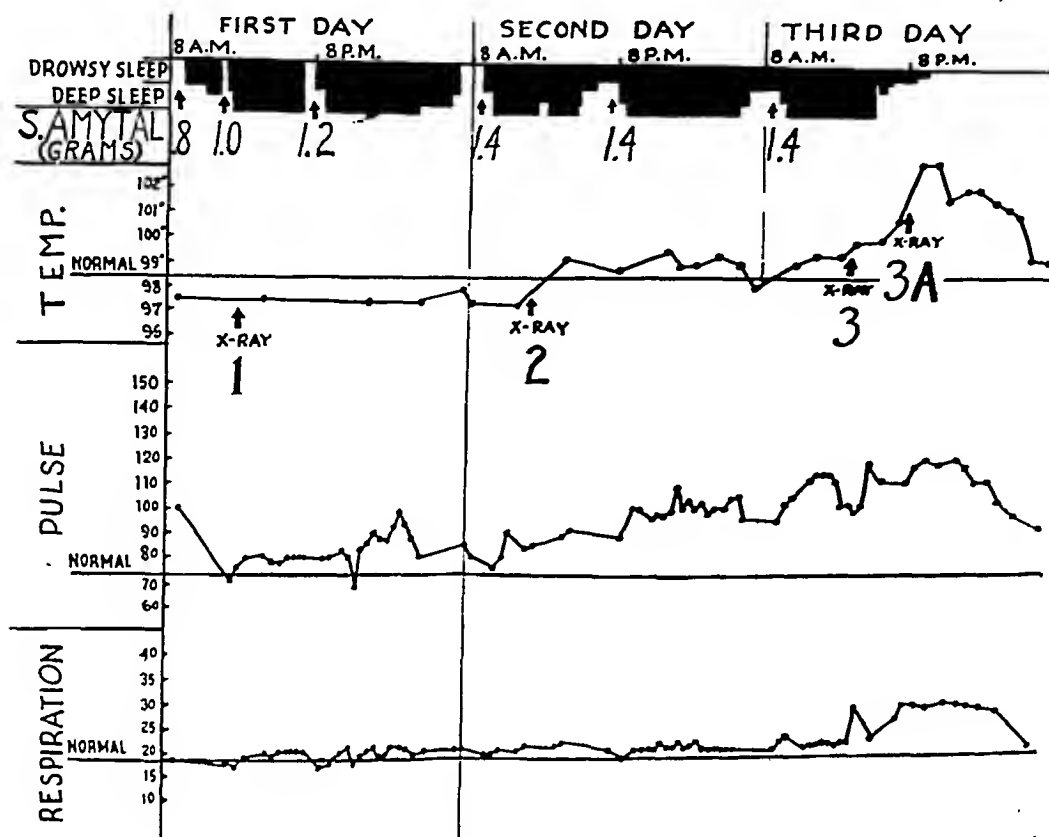


FIG. 19. The temperature chart of the patient illustrated in Figures 13 to 18. The arrows indicate when the x-rays were taken.

narcosis, shows that the density in the right lower lung field has increased and lies in the area occupied by the right middle lobe. The lung fields bilaterally show still further decrease in aeration. Figure 17, taken on the first postnarcosis day the day after Figure 16 was taken, shows the density in the right middle lobe gone and the diaphragm lower. The aeration is improved more on the left than on the right side. Figure 18 was made on the second postnarcosis day. Both lung fields are clear and well aerated.

The temperature, pulse and respiration chart for this patient (Fig. 19) shows the fever and increased respiratory rate which attended the pulmonary changes. The gen-

Observations on the Urine, Blood and Hydration. Daily urine tests were usually normal. Albumin, red blood cells, white blood cells or casts were very rarely present. Also, the specific gravity of the urine usually ranged between 1.010 and 1.015. White blood cell counts and sedimentation rates were determined in a number of patients with fevers. Some of these are to be seen in Table II. In only one patient (Case 28) was the sedimentation rate greater than normal and the slight increases in leukocytes were not impressive. In occasional blood studies on the patients not included in Table II no greater changes were observed. Detectable concentrations of the blood were shown to

be absent by daily hematocrit determinations in eight narcotized patients who received 1,500 cc. of fluid daily in addition to their regular diet. This is considered to rule out dehydration as a cause of fever in our patients, since with rare exception all

mask. It was found, however, that an equal increase in the depth of respirations occurred when the rebreathing bag was removed from the mask or when the oxygen was furnished from a basal metabolic machine and the expired carbon dioxide

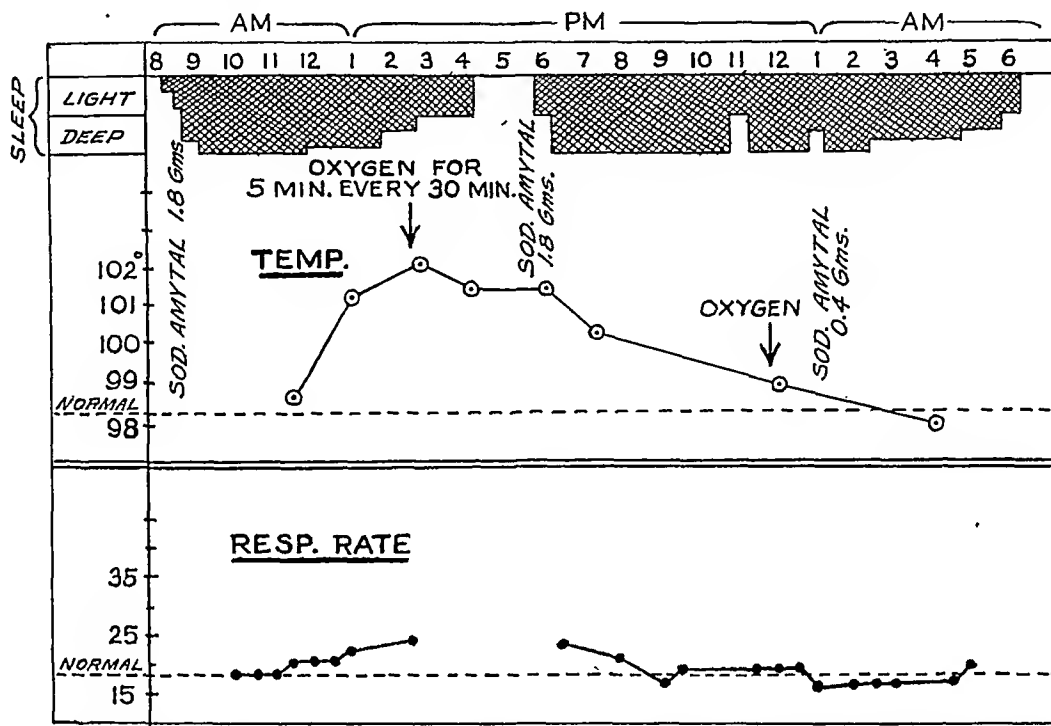


FIG. 20. Illustration of the results of frequent vertical posture and inhalation of 100 per cent oxygen for five minutes every thirty minutes on atelectasis. Both treatments were initiated at the highest point of the temperature at the first arrow and discontinued at the second arrow. Note that the narcosis treatment was not interrupted.

patients received 1,500 cc. or more fluid daily.

Treatment of Atelectasis in Narcotized Patients. The usual precautions were taken to prevent the development of atelectasis. The patients were turned frequently and fed cautiously. Also, all patients were "walked" supported by several assistants to the toilet to void several times daily and nightly. It was our impression that this procedure very effectively reduced the incidence of atelectasis.

It was also found that the breathing of 100 per cent oxygen increased the depth of breathing of deeply narcotized and cyanotic patients. The oxygen was usually administered with a Boothby rebreathing type of

mask. It was found, however, that an equal increase in the depth of respirations occurred when the rebreathing bag was removed from the mask or when the oxygen was furnished from a basal metabolic machine and the expired carbon dioxide was absorbed by soda lime. Furthermore, the addition of 5 per cent carbon dioxide to the oxygen or rebreathing to allow carbon dioxide to accumulate, did not stimulate respirations more than the breathing of oxygen alone in our deeply narcotized cyanotic patients. It should be mentioned that an increase in respirations was observed to follow disappearance of the cyanosis rather than precede it.

These same procedures were used to re-expand the lungs after atelectasis had developed. Patients were given oxygen to breathe for five minutes every thirty minutes or continuously and were held vertically for five minutes every thirty to sixty minutes. Figure 20 illustrates a fall in fever

which occurred in one patient after all of these procedures were used. Since such falls in fever have also been observed spontaneously, one cannot be certain that a cause-and-effect relationship existed in this instance. The results of many such experiences, however, indicate a very favorable effect of these maneuvers upon atelectasis in narcotized patients.

In a number of patients 5 per cent carbon dioxide plus 95 per cent oxygen was administered for five minutes every thirty minutes with the Boothby rebreathing mask. This increased the secretion of mucus to the point that the mouth and pharynx needed to be suctioned frequently to keep the airways free. Fevers appeared to be more frequent in these than in other patients. This point was not controlled statistically. It should be noted that the breathing of oxygen alone was not attended by an excess of mucus.

COMMENTS

Two types of pulmonary changes were observed during deep sodium amytal narcosis. First, all patients exhibited a generalized and uniform decrease in aeration of the lungs, accompanied by symmetrical elevation of the diaphragm and collapse of the chest cage. Second, many patients (eighteen of twenty-eight patients carefully studied) also exhibited focal pulmonary changes of variable appearance, accompanied by asymmetrical collapse of the chest and asymmetrical elevation of the diaphragm. Some focal lesions showed up in x-ray films as irregular hazy densities, some as linear shadows and one occupied the middle lobe and resembled pneumonia. Except for the very transient character of these lesions, they could easily have been confused with atypical pneumonia, which was observed frequently in troops in that area. Fever was present at one time or another in nearly all patients but as a rule the tempera-

tures were higher in patients with both focal and general lung changes.

All pulmonary changes were relatively transient. The focal lesions usually disappeared in a few to twenty-four hours but in two patients the lesions remained after narcosis for two and four days, respectively. They were also observed to shift from one lung to another, possibly as the result of posture. These facts, plus the asymmetrical changes in the diaphragms and chest wall and the absence of indications of infection, are compatible with atelectasis of a lobular or segmental variety.

Our observations suggest that the changes leading to this atelectasis developed according to a definite pattern. Decreased aeration of the lungs was the first detectable change. It appeared to be due to a uniform compression of lung tissue by the collapsed chest and high diaphragm. Possibly some vascular stasis or congestion contributed to this picture of generalized increased density since a high diaphragm alone may not produce it. In a few instances a slight asymmetrical elevation of one half of the diaphragm was observed without detectable pulmonary changes. Perhaps focal changes were present in these patients but were not seen because they were slight or because they were obscured by other structures. Gross focal pulmonary lesions developed next, signifying complete or nearly complete collapse of one or more pulmonary segments. This was observed in about 65 per cent of the carefully studied patients.

The mechanism of massive collapse of one or more pulmonary lobes, following obstruction of their main lobe bronchi by foreign bodies or mucus plugs, is not difficult to demonstrate. In animals such an obstruction internally by a foreign body^{7,8} or externally by ligature^{8,9} is followed by absorption of all the air from the obstructed lung tissue in from two to twenty-four hours. Some of the gas may be removed as the result of ciliary

action when the bronchus is plugged by mucus¹⁰ but most or all of the air is probably removed by way of the blood stream. If the obstruction is incomplete a ball-valve opening may cause emphysema instead of atelectasis.⁸

The mechanism of the development of lobular atelectasis is less clear. Experimentally, Van Allen¹¹⁻¹³ has shown that obstruction of secondary and smaller bronchi and bronchioles does not cause collapse of lung tissue as long as air passes freely to any portion of the involved lung lobe. In all probability this is due to a free passage of air between adjacent alveoli by way of small anatomical ostia.¹⁴ This exchange of air between adjacent normally aerated and obstructed lung lobules may be sufficient to prevent collapse of otherwise isolated alveoli in the dog.

In view of Van Allen's findings, one would not expect atelectasis to follow simple obstruction of a few small bronchi and bronchioles. It is apparent that factors other than obstruction must be present or that lobular atelectasis is produced by other mechanisms. Compression by a pneumothorax can produce atelectasis. Also, areas of atelectasis have been produced experimentally in emphysematous lungs by pressure of the vertebral bodies on over-riding lung tissue.⁸ In this latter instance the atelectasis was confined to the compressed areas. In our deeply narcotized patients the atelectasis was usually in the midlung tissue; there were no lesions confined to the surface to suggest that pressure alone had been their cause.

It is believed that the atelectasis which develops during deep narcosis is not due to compression alone. However, it is clear that the elevation of and reduced excursion of the diaphragm, together with collapse of the chest, are prime factors in its development. First, in deep narcosis the lungs are reduced in volume to a degree commensurate with

extreme expiration. A similar although probably smaller decrease in lung volume is present postoperatively.¹⁵ In the expiratory phase of respiration the bronchi and larger bronchioles are reduced in diameter¹⁶ and consequently can be easily obstructed. Furthermore, the processes which keep the air passages patent are interfered with and mucus accumulates. The ciliary action is less effective than normal; a smaller and weaker stream of air passes through the air ways; coughing is absent or ineffective.¹⁷ Second, this partial "collapse" of the lung interferes with the collateral exchange of air between adjacent lung lobules, to the extent that absorption of air by the blood exceeds its entry into blocked alveoli from adjacent normal alveoli. Van Allen found that atelectasis occurred after the occlusion of bronchioles and smaller bronchi if the breathing was forced or difficult, either from stenosis of the trachea or for other reasons. It failed to develop, however, when the breathing was free. Probably the small interalveolar ostia are reduced in size or even obstructed by a reduction in the volume of the lungs much as the airways are reduced in diameter. This is suggested by the fact that these interalveoli ostia are much easier to demonstrate microscopically in expanded than in collapsed lung tissue.¹⁴

Another factor of debatable and possible of great importance is anoxia. Drinker and his collaborators¹⁸ have shown that the flow of lymph from the lungs of dogs is increased by anoxia. This indicates that there is an excess of fluid in the respiratory bronchioles and distalward. Practically all of our narcotized patients exhibited varying degrees of cyanosis of mucous membranes and nail beds which could be readily changed to normal by the breathing of oxygen. Quite possibly this anoxia increased the amount of fluid in the smaller airways and contributed to their obstruction. The inclusion of carbon dioxide with oxygen in breathing mixtures

when rebreathing types of masks were used apparently caused even a greater outpouring of mucus, much of which appeared in the larger airways and was removed by suction. This is in accord with other experiments of Drinker and his collaborators which demonstrated that the flow of lymph from the lungs of dogs was greatly increased by elevation of the concentration of carbon dioxide in the breathing mixture above normal levels.* Anoxia also appeared to be a factor in maintaining a depression of respiration in our patients. This is suggested by the fact that the breathing of oxygen for three to ten minutes resulted in an increase in the depth of breathing which was usually not sustained after the oxygen had been discontinued.

Lobular atelectasis, often transient, develops in a variety of conditions, in all of which the volume of the lungs and the ventilation are significantly diminished. Pasteur¹⁹ seems to have first called attention to this in diphtheria. He noted collapse of the lower lobes of the lungs in fifteen of thirty-four severely paralyzed diphtheria patients. He made the diagnosis clinically by the presence of (1) increased movements of the lower ribs, (2) reversed movements of the epigastrium during respiration and (3) altered character of the voice and cough. He attributed this atelectasis to paralysis of respiration which allowed the lungs to collapse as the result of their normal elasticity. Pulmonary complications have been observed frequently in acute infectious polyneuritis²⁰ and in acute poliomyelitis.²¹ In both instances hypoventilation due to paralysis appears to have been the important factor. Briscoe^{22,23} noted atelectasis in a variety of conditions in which breathing

was diminished, either due to paralysis of the muscles of respiration or generalized debility. Linear opacities, which often disappeared after deep breathing, were described by Fleischner^{24,25} and were later confirmed.²⁶ These were thought to be due to shallow breathing from pain, as the result of inflammation near the diaphragm or by generalized debility. In three patients the atelectasis was verified histologically. One wonders how frequently atelectasis is the forerunner of terminal pneumonia when the diaphragms are elevated and restricted in movement by ascites or other abdominal masses. It is not unlikely that it precedes pneumonia in paralyzed and debilitated individuals far more frequently than is recognized.

Transient lobular atelectasis has been noted postoperatively.²⁷⁻²² The very marked depression of respiration in deep narcosis with reduced tidal air and vital capacity, collapsed chest and high diaphragm are changes which are also present postoperatively.³³⁻³⁹ Thus, in operations for the repair of inguinal hernia, the incidence of atelectasis has been reported to be roughly 3 per cent; after general abdominal operations 14 per cent and after gastric and duodenal operations approximately 42 per cent.^{29,30} The reduction in pulmonary ventilation after operations outside of, or in the lower part of the abdomen or in the chest, is usually about 50 per cent. After upper abdominal operations, however, the reduction in ventilation is even more and has been reported as great as 78 per cent.³⁴ It is of interest to note that atelectasis has occurred twice as frequently after local or spinal anesthesia as after general anesthesia when given for herniorrhaphy.³⁰

Re-expansion of the lungs and aeration of the collapsed alveoli has been attempted in a variety of ways depending upon circumstances. When the condition persists a respirator of the Drinker type is probably

* Recent experiments in sodium amytal narcotized dogs have shown that the fall in arterial oxygen saturation is accompanied by a parallel increase in the carbon dioxide content of the arterial blood. This may have been a more important factor in producing an excess of fluid in the pulmonary airways than anoxia.

of greatest usefulness. Smith⁴⁰ believed that reduced vital capacity in poliomyelitis was an indication for the use of a respirator of this type. He stated that the ability to breathe was not sufficient indication to remove a patient from the respirator, but that the patient must also be able to cough effectively. Cooperstock²¹ has also warned about the too early removal of patients from the respirator. Zollinger³⁸ has attempted to increase the vital capacity in postoperative patients by injecting the intercostal nerves which supply the operative field with prolonged anesthetic agents. This procedure appeared to increase the vital capacity and he thought that it decreased the incidence of pulmonary complications. We have employed the same basic principles of treatment; namely, an attempt to reexpand the lungs. The most potent of our procedures was postural and consisted of holding the patient in a vertical position for periods of five to ten minutes. The effect of vertical posture in increasing inspiration has been shown by a recent study.¹ In comatose⁴ patients a fairly satisfactory tidal air and adequate pulmonary ventilation can be obtained by the Eve tilt method of artificial respiration. At best, such methods are temporary expedients and can only be useful when the mechanisms producing collapse will be dissipated or lessened in a few hours.

Our second procedure consisted in the breathing of oxygen periodically. This was followed by a gradual increase in the depth of breathing, even when carbon dioxide was not included or was not allowed to accumulate in the breathing mixture. No greater increase in ventilation was obtained by the addition of carbon dioxide to the mixture. Henderson⁴² has pointed out the unusual and variable responses of barbiturate narcotized patients and animals to the breathing of oxygen and carbon dioxide-oxygen mixtures.⁴³ Our experiences are in accord with these observations. A further discussion

of the mechanisms involved are, however, beyond the scope of this paper. Intravenous glucose solutions were occasionally helpful, in that they lightened narcosis and in this indirect way increased the depth of breathing.

The mechanism of the fever that accompanies reduced aeration of the lungs with or without atelectasis is not clear. The absence of leukocytosis and the presence of normal sedimentation rates render infection unlikely. Another physiologic mechanism is suggested by the clinical findings of hypoventilation, cold skin and low blood pressure; namely, a lessened heat loss, first from the lungs as a result of hypoventilation and second, from the surface of the body as a result of peripheral vascular collapse. Such a mechanism could result from central depression by the sodium amytal. The twice daily and concomitant fluctuations in the depth of narcosis, fever, hypoventilation and tendency to low blood pressure favor such an explanation.

SUMMARY AND CONCLUSIONS

A group of patients with combat exhaustion, who were being treated with continuous sodium amytal narcosis, exhibited uniform decreased aeration of the lungs accompanied by symmetrical elevation of the diaphragm, collapse of the chest, reduced tidal air and cyanosis. Approximately 65 per cent of these patients also showed transient patchy and irregular densities in the lungs, accompanied by asymmetrical elevation of the diaphragm and slight asymmetry of the chest cage. The focal lung changes were interpreted as atelectasis.

During the first twelve hours of deep narcosis the body temperature usually fell 1 to 2 degrees Fahrenheit. Subsequently, it rose and was higher on the second and third than on the first day. In patients with focal, as well as general lung changes, the fever was usually higher than in those

exhibiting decreased aeration alone. Significant changes in respirations during fever occurred in only a few patients with marked pulmonary lesions. There was a direct correlation between the degree and frequency of fever and depth of narcosis.

The mechanism of the pulmonary changes appears to be, first, compression of lung tissue due to a collapsed chest and high diaphragm; this decreases the diameter of the smaller airways and probably lessens or stops the collateral circulation of air from one to another alveolus by way of the inter-alveolar ostia. Second, the smaller airways become blocked and lobular atelectasis develops. Anoxia and hypercapnia contribute to this by increasing the fluid content of the smaller airways.

The mechanism of the fever is probably not infectious. It is suggested that a failure of heat loss through the lungs as a result of hypoventilation and from the skin as the result of cutaneous vascular insufficiency is one factor in the production of fever in these patients. The deeply narcotized and cyanotic patients usually exhibited an increased depth of respirations when given 100 per cent oxygen to breathe. This was preceded by a clearing of the cyanosis. The presence of carbon dioxide (5 per cent) in the breathing mixture or its accumulation as the result of rebreathing did not stimulate respirations more than the breathing of oxygen alone.

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Prognosis in Gastric Cancer*

A Study of Five-year Survivors

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IN a series of 466 patients with gastric cancer admitted to the University Clinics from 1927 to 1944, 389 (83.5 per cent) underwent operation, 203 (43.5 per cent) being subjected to resection of various types; 150 (32.8 per cent) survived resection.¹ Of the total 466, 377 were seen in the years from 1927 to 1941 and hence were suitable for a study of subsequent course; of these 155 (41.1 per cent) underwent resection and 115 survived. The purpose of this paper is to report a further study of the factors responsible for prolonged survival.

Detailed follow-up was made in 93 (80.8 per cent) of the 115 survivors. Sixty-five (56.8 per cent) were found to have died; twenty-eight during the first post-operative year, twenty-four in the second, seven in the third, five in the fourth and one in the fifth. Twenty-eight patients, constituting 7.4 per cent of the 377, 24 per cent of the 115 or 30 per cent of the ninety-three, survived five years or longer. Walters, Gray and Priestly² found 28.9 per cent of 2,322 resection survivors to live five years or more after operation, Custer³ 27 per cent, Livingston and Pack⁴ 25 per cent and Weese⁵ 19 per cent. Thus, the five-year survival rate of the patients successfully withstanding gastrectomy for gastric cancer varies from 19 to 30 per cent. In Weese's group this constituted 7.59 per cent of all patients, whereas in Oughterson's⁶ and in Mage's⁷ groups it was approximately 2 per cent. Increased operability and decreased mortality should mean an increase in the

number of five-year survivors. However, this may not be the case because of the law of diminishing return. Allen⁸ found that as the operability increased 10 per cent and the mortality decreased 10 per cent the number of five-year survivors increased only 1 per cent.

TABLE I
AGE INCIDENCE

	21-30	31-40	41-50	51-60	61-70 and over
Original group.	0.6%	4.6%	18.5%	34%	42.3%
Five-year survivors. . . .	0	6.6%	40%	16.6%	36.6%

In addition to the twenty-eight five-year survivors, two who lived four years and nine months have been incorporated into the study, making a total of thirty.

Sex and Age. In a previously reported analysis of 466 cases of gastric carcinoma, the initial group from which the present survivors were obtained, 70 per cent were males. Of the thirty survivors 60 per cent were males, indicating that the survival rate in males is the same or slightly less than in females. The incidence of death from cancer of all types among males has increased more rapidly than in females according to a survey by Collins⁹ and his collaborators.

Table I contrasts the age distribution in the survivor group with that of the original group in which the incidence of gastric cancer clearly rose from decade to

* From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago, Ill.

decade. The irregular distribution in survival incidence with peaks in the fifth and seventh decades and a slump in the sixth is difficult to explain except on the basis of chance due to the small number of cases. Walters, Gray and Priestly² noted a higher

TABLE II
DURATION OF SYMPTOMS

	1-3 mo.	3-6 mo.	6-12 mo.	12-24 mo.	Over 24 mo.
Original series . . .	24.5 %	18 %	26.2 %	11.9 %	19.1 %
Five-year survivors . . .	23.3 %	3.3 %	23.3 %	20 %	30 %

proportion of five-year survivors in the sixth and seventh decades, the lowest survival rate being in patients below forty-years of age.

SYMPTOMS

Duration of Symptoms. As shown in Table II 68.7 per cent of the original group had symptoms of less than one year's duration as compared with 50 per cent in the five-year survivors. In the former 42½ per cent had symptoms of less than six months' duration in contrast to 26.6 per cent of the latter. The group with symptoms of twenty-four months' duration or longer had a relatively better prognosis than those with symptoms of less than six months at the time of resection. Saypol and Hinton¹⁰ found the resectability rate to be higher in those patients with symptoms of over six months than in those under six months. Walters *et al.* noted the five-year survival rate to be 24.6 per cent in those patients with symptoms of less than a year's duration and 32.1 per cent in those with symptoms of more than a year's duration. Faged and Larsen¹¹ in reporting upon 375 patients noted that 64 per cent had had symptoms of less than six months' duration; nevertheless, 50 per cent of these were inoperable at the time of first examination. These observations raise the question of the validity of the great emphasis placed on "early diagnosis." Symptoms depend upon

many factors, such as location, obstruction, ulceration and anemia. It is a well recognized fact, of course, that gastric cancer may be far advanced before symptoms appear. Informative propaganda may bring the patient to the physician somewhat earlier; a good economic status may make for earlier diagnosis; however, these factors seem of minor importance compared with that of the fundamental biologic characteristics of the tumor.

Type of Symptoms. In the present group of thirty patients upper abdominal digestive distress was the chief complaint, being present in 93.3 per cent of the cases. In many, the distress was insidious in onset, unrelated or indefinitely related to food consumption and often inconstant in character. In some, the history suggested peptic ulcer, with periods of improvement noted after institution of ulcer therapy. Twenty-four described weight losses averaging from 10 to 20 pounds in a period of two to twelve months. Anorexia was marked in twelve patients. Three had no gastrointestinal complaints, presenting themselves with weakness and fatigue. Two noted tarry stools. These are the usual symptoms of gastric cancer and indicate that there are no special distinguishing symptoms in five-year survivors as compared with those who fail to survive. Saypol and Hinton¹⁰ report the incidence of pain and digestive distress as 76.2 per cent and weight loss as 71.8 per cent.

PHYSICAL EXAMINATION

Palpable epigastric tumor masses were noted in 26.6 per cent of the five-year survivors as compared with 40 per cent in the original group. It is evident that large neoplasms are not a contraindication to surgical resection and, indeed, offer a fair prognosis. Lemon-tinged skin was marked in three patients. The liver was palpable but smooth in two. No lymph node involvement was detected in any of the group. Epigastric tenderness on palpation, a rather equivocal and unimportant finding, was present in eleven (36 per cent).

Anemia, Blood Loss and Gastric Acidity. Table III indicates that in thirty, five-year survivors at the time of initial examination four or 13.4 per cent had erythrocyte values below three million, thirteen or 43 per cent below 4 million, twelve or 40 per cent be-

TABLE III
ABSENCE OF RELATIONSHIP OF ERYTHROCYTE LEVELS TO
THE TYPE OF TUMOR

Erythrocyte Level	Type I	Type II	Type III	Total
2-3 million	2	2	..	4
3-4 million	4	8	1	13
4-5 million	3	6	3	12
Over 5 million	1	..	1
Total	9	17	4	30

tween 4 and 5 million and one or 3 per cent over 5 million. Nine or 30 per cent exhibited hyperchromic, seven or 23.3 per cent hypochromic and fourteen or 46.6 per cent normochromic blood pictures. Of the four patients with levels below three million no gastric free acidity on histamine stimulation was found in four; the stools, after meat-free diet, contained large amounts of occult blood as shown by the benzidine test. Polypoid ulcerated type I* carcinoma was present in two and type II in two others. In thirteen patients with values between three and four millions four were type I, eight others were type II while one was type III. The stools of nine were strongly positive with benzidine, three disclosed a trace and one had no blood. Of the last four patients three had type II and one type I carcinoma. Acid gastric juice was found with equal frequency in both types. In the twelve patients with red cell levels above four million there were six type II, three type I and three type III carcinomas.

The stools of twenty-five patients were examined for occult blood by the benzidine test. In all instances the patients were placed on a meat-free diet for three days

before the stools were collected and three or more specimens were examined. Large amounts of occult blood were found in fourteen, a trace only in eight and none in three. The degree of anemia, the presence or absence of occult blood and the level of gastric secretion was of little or no prognostic value as was shown by the five-year survival. The patients with polypoid lesions, however, did tend to be the most anemic.

Roentgenologic and Gastroscopic Manifestations. All of the thirty tumors were considered resectable by the roentgenologist. The operative findings confirmed the fluoroscopic and film diagnosis as to the site of the lesion: fourteen were antral, fourteen mid-gastric and two cardiac. Of the antral lesions two were type I Borrmann, nine type II and three type III. In the mid-stomach six were type I, seven type II and one type III. Of the two cardiac lesions one was type I and the second type II. The number of "curable" cancers found in the antrum was approximately the same as those found in the mid-stomach.

It is worth noting that in 20 per cent the initial x-ray findings were inconclusive in this group as compared with 8 per cent in the original group, thus suggesting earlier diagnosis and smaller lesions although subsequent measurements of the tumor apparently do not substantiate this point. Likewise in the survival group the initial gastroscopic examination was unsatisfactory in 40 per cent as compared with 15 per cent in the original group.

Gastroscopy disclosed the presence of atrophic gastritis in seven patients, in five it was absent and in six it was not recorded. Meissner¹² found the incidence of gastritis in patients with gastric cancer to be similar to that of patients with ulcer. The body and the fundus, however, were more often involved by the process.

DIFFERENTIATION FROM BENIGN ULCER

Allen in following a series of gastric ulcers over a ten-year period found that 14 per cent eventually proved to be carcinoma. Holman and Sandusky,¹³ in a

* Gross classification of Borrmann, types I to IV inclusive.

study of 53 patients with gastric ulcer and 104 with carcinoma of the stomach, noted that the differentiation of ulcerating carcinoma and benign ulcer was not possible in 33 cases. Even at operation, in 23 of the 157 patients, the surgeon could not determine the true nature of the lesion. The problem of differentiation of the two lesions is not pertinent to this paper except to remark that in our series, as in all series, carcinomas were observed masquerading as benign ulcers. Some of the factors operative in such cases have been discussed elsewhere.¹⁴

TYPE OF TUMOR

The importance of the rate of growth, dependent upon unknown factors but obviously varying from cancer to cancer, is illustrated by the following cases:

One patient¹⁵ was followed four and one-half years before assenting to laparotomy. During this period many x-ray and gastroscopic examinations disclosed an unusual lesser curvature ulcer which at times appeared benign and on other occasions looked like an ulcerating carcinoma. Histologically, the lesion was a well circumscribed colloid carcinoma. This case is an example of a slowly growing, almost benign carcinoma.

A second patient with a polypoid tumor of the antrum was observed for three years prior to operation. Repeated roentgenographic and gastroscopic examinations failed to reveal any significant change in the appearance of the lesion. Microscopic study revealed an adenomatous polyp with malignant changes. Apparently the rate of growth of the neoplastic tissue was an extremely slow one.

In contrast, one may cite the following case not included in this series in which a suspicious lesser curvature defect was demonstrated in a fifty-two year old male with symptoms suggestive of ulcer; exploration was advised but refused; a second examination two months later disclosed some decrease in the size of the lesion. Three months later, five months after the initial examination, both x-ray and gastroscopy

demonstrated a large tumor mass in the mid-stomach and operation revealed an inoperable type iv carcinoma with liver metastases.

In 20 per cent of five-year resection survivors indefinite findings or other factors resulted in a delay of three months to four and one-half years before operation, yet all survived five years or more after resection. This further emphasizes the importance of the innate character of the tumor.

When the thirty five-year survivors are grouped according to the gross classification of Bormann (seen in the illustration on page 234), twenty-six fall into types I and II, a finding in accord with others and in contrast to the total incidence of the various types as described by Schindler: 2.99 per cent type I, 17.6 per cent type II, 16.3 per cent type III and 63.2 per cent type IV. This apparently suggests that the gross, or Bormann, classification may be of considerable prognostic value. In a comparison of the five-year survivors with a group who survived for less than one year after resection, however, the correlation was not as striking. Histologic studies of the two groups were then made and are being reported in detail elsewhere.¹⁵




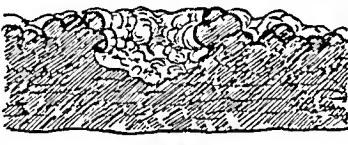
In general the tumors resected from patients who survived five years or more tended to be sharply circumscribed. In an occasional case the tumor cells showed marked degenerative changes resembling those of prostatic carcinoma after orchiectomy. Histologically, the tumors from the five-year survivors were of all types, including adenocarcinoma, fourteen; undifferentiated carcinoma, six; round cell carcinoma, three; colloid carcinoma, three; mixed cell carcinoma, three and infiltrating carcinoma, one. In contrast, the group who survived less than one year contained eleven infiltrative lesions. This illustrates again the tremendous importance of the inherent nature of the tumor itself.

A comparison of the sizes of the lesions in the different groups showed surprisingly little variation. Nine type I tumors varied from 10 by 9 by 6 cm. to 1.5 by 1.5 by 2

cm., with a mean of 5 by 5 by 7 cm. Seventeen type II tumors ranged from 9 by 6.5 in diameter to 1.5 by 2 cm., averaging 7 by 5 cm. Four type III lesions averaged 4 cm. in diameter. MacCarty¹⁷ found the mean diameter of a large group of resected

tumor metastases to the transverse colon by a type II lesion survived partial gastrectomy and partial colectomy and was well ten years later.

In two patients at operation the stomach was found attached to the liver, necessitat-

Gross Classification of Gastric Carcinoma - BORRMANN		Incidence in all gastric Ca.	Incidence in 30 5 year survivors
TYPE			
I		2.9 %	30. % (9 cases)
II		17.6 %	56.8 % (17 cases)
III		16.3 %	6.66 % (4 cases)
IV		63.2 %	0

Prognosis in gastric cancer.

lesions to be 6 cm. with a slight decrease in the size of those encountered in the later years of his study. Our study suggests that the size of the lesion is of little importance in determining the degree of malignancy or life expectancy. Apparently even the "curable" cancer approaches 6 cm. in diameter before detection.

Seven or 23 per cent of the survivors had evidence of lymph node metastases, mesenteric involvement or spread to the neighboring organs at the time of operation. Of six with lymph node involvement five were type II and one was type I Borrmann. Survival after resection was more than five years in one, seven years in three and eleven years in a fifth. A sixth (type I) with mesenteric involvement at the time of partial gastric resection developed recurrence in the gastric stump with involvement of the liver twelve years later.¹⁸ The seventh with

ing resection of a portion of that organ, averaging 5 by 5 by 3 cm. in each case. Histologic examination showed only inflammatory reaction and no evidence of liver metastases. Here the importance of removing carcinoma with resection of the liver, when feasible, is demonstrated. The desirability of palliative resection when portions of neoplastic tissue are knowingly left behind is considerable. Anschütz¹⁹ reported that 21 per cent of ninety-nine such patients survived three years and 8 per cent survived five years, in contrast to death within one year as occurred in untreated patients.

POSTOPERATIVE STATUS

Two of the thirty patients (6.6 per cent) developed marked anemia. The first, with a type II tumor of the antrum necessitating removal of the distal half of the stomach,

had on admission a free acid value of 50 clinical units and an erythrocyte count of 3.8 million with 12 Gm. of hemoglobin. The anemia, which developed postoperatively, (3 million red cells and 10 Gm. hemoglobin), was at first considered due to an inadequate diet; however, there was no response to parenteral liver, iron or diet. Four years later the erythrocyte and hemoglobin values were unchanged. The second, a fifty-six year old male had on admission red cell count of 3.9 million with 13 Gm. of hemoglobin. A 5 by 3 cm. type II carcinoma of the posterior antral wall was found at laparotomy and the distal two-thirds of the stomach was resected. After operation the erythrocyte level declined to less than 3 million. The patient responded favorably to parenteral liver extract and has maintained an erythrocyte level of over 4.5 million with this therapy.

Two patients were known to have pernicious anemia before resection. One had been followed in the Hematology Clinic for three years when he noted a mass in the left upper abdomen. Laparotomy proved this to be a type I carcinoma 10 cm. in diameter; the lower two-thirds of the stomach was resected. The patient has been adequately maintained on liver extract for four years and nine months after operation with no apparent ill effect from gastrectomy. A second patient previously described¹⁸ was found to have pernicious anemia and a polypoid gastric lesion. At operation six months later this was removed and found to be a polypoid adenocarcinoma with myxomatous degeneration. Eight years later a type I carcinoma necessitated partial resection of the stomach. Nine years after the resection gastroscopy disclosed several polyps in the remaining stomach; three years later, twenty years after the first operation and twelve years after the second, recurrence of the lesion with metastases necessitated a third operation which the patient did not survive.

One patient with total gastrectomy was among the five-year survivors. On admission his red count was 3.84 million and

hemoglobin 7.4 Gm. No free acid was present on histamine stimulation. A large type I cardiac lesion required removal of the entire stomach with splenectomy. Local lymph node metastases were present. The patient has remained in good health with no evidence of anemia or digestive disturbances in the five years following operation. Joll and Adler,²⁰ in reporting two cases surviving three years and two months and three years and six months, respectively, following total gastrectomy, found records of forty-seven others described between 1933 and 1942.

In a study of the economic status of the group it was found that eighteen had no symptoms and were self-sustaining economically. Six others complained of moderate to severe digestive disturbances which limited their working capacity but allowed economic independence. Two had persistent fatigue and failed to gain weight but were able to support themselves partially. Two others developed myocardial infarcts. One had coronary insufficiency for many years and survived a gastric resection for seven years. He remained a chronic invalid during the entire postoperative period and died following cardiac infarction. The second survived infarction three years after gastrectomy and has been able to carry out a fair portion of his duties.

Two patients developed recurrent carcinoma six and nine years, respectively, after resection. The former, a forty-one year old housewife, was subjected to subtotal gastrectomy eighteen months after the onset of digestive symptoms. A second operation six years later revealed metastases to the ovaries, a Krukenberg's tumor. The stomach was not involved. The latter patient¹⁸ has been previously described. Here the lesion was confined to the stomach.

Eighty per cent (twenty-four) of the survivors were restored to useful life for five years or more after operation.

SUMMARY

Of 377 patients with gastric carcinoma 115 or 30.8 per cent survived resection;

twenty-eight, 7.4 per cent of the 377, survived five years.

Fifty per cent of the five year survivors had had symptoms of over a year's duration as compared with 31 per cent of the initial group. The symptoms were essentially identical in type. Palpable tumor masses were present in 40 per cent of the original group as compared with 26.6 per cent of the survivor group.

Nine of the survivors had type I (Borrmann) carcinoma, seventeen had type II and four had type III; there were no five-year survivors in the Borrmann type IV group.

Metastases were present in 23 per cent of the five-year survivors, five with lymph node involvement, one with mesenteric involvement and a seventh with spread to the transverse colon.

Eighty per cent of the five-year survivors were restored to useful life.

CONCLUSIONS

1. Contrary to what might be expected in gastric cancer, patients with symptoms of long duration tend to show a higher percentage of five-year survival than do those with symptoms of short duration.

2. Presence of a palpable tumor mass is not a contraindication to operation or resection.

3. The initial erythrocyte values, hemoglobin levels and gastric free acidity have no prognostic import.

4. The type of carcinoma is of the greatest prognostic significance, the long survivors consisting chiefly of those with type I and type II tumors (Borrmann).

5. The size of the lesion varies widely even in "curable" cases.

6. The need for further study of the factors responsible for the variable rate of growth in different tumors is evident. The rate of growth is the most important factor in determining the duration of survival. This fundamental problem is, of course,

inseparably linked with that of the cause of cancer.

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Benign Pelvic Tumors with Ascites and Hydrothorax*

Meigs' Syndrome

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THE syndrome of fibroma of the ovary associated with ascites and hydrothorax is one which has only recently been brought to the attention of the internist, gynecologist and surgeon through the work of Meigs and associates.²⁻⁷ The importance of a thorough knowledge of this condition is at once apparent since a tumor giving rise to distant effusions has heretofore been associated with grave prognostic implications and has usually carried a stigma of inoperability.

The first account of this syndrome was published by Cullingsworth¹ in 1879. His patient complained of masses in the lower abdomen and of uterine hemorrhage. Later her abdomen began to swell, she lost weight, developed a left pleural effusion, became intensely dyspneic and, after three months, died. Operation was considered to be unwarranted. How many more such cases occurred and are occurring without their true significance being recognized may only be speculated upon. It is encouraging, however, that recognition of this syndrome is now growing because, following Cullingsworth's report, only five more cases were described before 1932 and since that time some fifty to sixty cases have been added to the literature. This has been due chiefly to the orderly work of Meigs and his group which was first published in 1937 although previous observers in recent times such as Leco in 1926¹⁰ and Salmon¹² knew of this syndrome. On the basis of these reported cases it has been shown that this syndrome usually occurs in women past the menopause. The symptoms have chiefly been dyspnea and swelling of the abdomen although weakness, chest and abdominal pain and cough have been present; the

duration of symptoms ran from a few days to several years in one of Meigs' cases.⁵ The location of the tumor has been about equally divided between the two sides and in about 10 per cent of cases has been bilateral. The pleural effusion has usually been on the right side. In 10 per cent of the cases it has occurred only on the left while in 15 per cent the effusion has been bilateral.

In 1943 Rhoads and Terrill¹³ presented a case and first termed the condition "Meigs' Syndrome." This name has endured and justly gives credit where due; however, it has resulted in some confusion in nomenclature. Meigs' group has continued to include in the syndrome only a fibroma of the ovary. Others have broadened the term to include any benign pelvic tumor giving rise to ascites and to hydrothorax. We agree with the latter viewpoint since, so far as is known, the mechanism of the effusions remains the same regardless of the type of the tumor. Meigs' syndrome has, therefore, been reported to include thecomas²³⁻²⁵ myomas of the uterus,^{24,26} Brenner tumor²² and struma ovarii²⁴ as well as the ovarian fibromas as originally described. That the same syndrome may arise with pelvic malignancies without metastasis to the chest should be kept in mind.⁷

CASE REPORTS

CASE I. K. B., a fifty-two year old, single, practical nurse, entered the Barnes Hospital, June 9, 1943, with the complaint of dyspnea on exertion of two week's duration. During the same period she also complained of fatigue and a dull, aching pain in the lower left chest posteriorly. The chest pain and dyspnea appeared quite suddenly while she was walking and had never been present before.

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The family history was relevant in that a sister had pulmonary tuberculosis in 1934. The patient had intimate contact with this sister in the early stages of her disease.

The past history is of interest in that an operation was performed in 1939 at which time the uterus, right tube and right ovary were removed. The surgeon noted no abnormality of the left ovary at that time. There were never any symptoms suggestive of pulmonary tuberculosis. Normal menopause occurred at the age of forty-seven years. There had been a steady weight gain from 140 pounds at the age of thirty years to the present weight of 210 pounds.

Physical examination revealed a temperature of 36.5°C. (97.6°F.), pulse of 88 per minute and respirations of 20 per minute. The blood pressure was 150/92. The patient was generally obese. There was slight widening of the arteriolar reflexes of the retinal vessels. The tonsils showed moderate hypertrophy but were not inflamed. The chest was symmetrical with equal expansion of the two sides. There was marked dullness to percussion up to the fifth rib posteriorly on the right and impaired resonance up to the apex at which point a few moist râles were heard. On this side the percussion note was dull in the axilla and also up to the second rib anteriorly. Fremitus and breath sounds were decreased in intensity over this area but the character of the breath sounds was not changed. The left chest was entirely clear. The abdomen was soft and protuberant. There was no rigidity but there was tenderness over the right upper quadrant and over the left lower quadrant. Just above and to the left of the symphysis pubis was felt a slightly irregular, movable, firm, orange-sized mass. No signs of free fluid in the abdomen could be detected. Pelvic examination revealed a firm, non-tender mass in the left adnexal region which seemed to be continuous with the abdominal mass. A normal cervix with a polypoid structure protruding from the external os was visualized. Rectovaginal examination revealed a firm, freely movable mass, 6 to 8 cm. in diameter, high in the left adnexal region. There were numerous varicosities over both lower extremities.

Laboratory data revealed a complete blood count, urinalysis and stool examination to be normal. The Kahn test was negative, non-protein nitrogen was 18 mg. per cent and the fasting blood sugar 95 mg. per cent. The first strength PPD (tuberculin) test was negative

after forty-eight hours. The sedimentation index was 1.5 mm. per minute (Wintrobe). Total plasma proteins were 5.6 Gm. per cent, with albumin 3.5 Gm. per cent and globulin 2.1 Gm. per cent. Vital capacity was 1,925 cc. (probably submaximal due to chest pain). The venous pressure was 70 mm. of saline, the ether circulation time was 7 seconds and the decholin time 10 seconds.

Fluid was aspirated from the right chest on the third, fifth and tenth hospital days. The volumes of fluid withdrawn were 550 cc., 1,975 cc. and 500 cc., respectively. On the first two thoracenteses, the fluid was yellow, slightly turbid, with a specific gravity of 1.013 and a cell count (after hemolysis with 0.1 N HCl acid) of 60 lymphocytes per cu. mm. Microscopic section of these sediments revealed no malignant cells. Aerobic and anaerobic cultures of all three samples of fluid yielded no growth.

The third fluid was serosanguineous with a specific gravity of 1.018 and a cell count (after hemolysis with 0.1 N HCl acid) of 2,200 per cu. mm. Differential count of these cells revealed 65 per cent eosinophiles and 17 per cent lymphocytes; the remainder were degenerated leukocytes. A guinea pig injected with fluid from the first thoracentesis was negative for tuberculosis. Chest films, taken before the first and after the second thoracentesis, failed to reveal any lung lesions. (Fig. 1.)

With the above information at hand, a pre-operative diagnosis of Meigs' syndrome was made and the patient was transferred to the gynecologic service. At operation about 200 cc. to 300 cc. of clear, free abdominal fluid were encountered and the left ovary was found to be solid, smooth and the size of a small grapefruit. There was no evidence of metastases. A left salpingo-oophorectomy and conization of the cervix were performed by Dr. Carl Wegner. There was no ovarian tissue, as such, found in the mass, and grossly and microscopically it was a typical fibroma. Microscopic study revealed the tube to be normal.

The postoperative course was entirely uneventful. There was no clinical or fluoroscopic evidence of reaccumulation either of the pleural or abdominal effusions. A roentgenogram of the chest, taken fifteen weeks after operation (Fig. 1), showed no residual abnormalities. The patient resumed her duties as a practical nurse six weeks after the operation and has remained perfectly well ever since.



FIG. 1. X-rays of the chest of Case I. A, before the first thoracentesis; B, fifteen weeks postoperatively.

CASE II. E. L., a sixty-four year old widow, was seen in the Washington University Clinics on September 10, 1946, and was admitted to the Barnes Hospital the following day with complaints of enlargement of her abdomen of nine months' duration and of dyspnea on exertion for four or five months' duration. She had no other symptoms except loss of appetite, a weight loss of 15 pounds during the past six months and a slight non-productive cough of a few months duration. The enlargement of the abdomen had been painless. Just prior to the appearance of dyspnea she saw her family doctor who told her that she had a tumor of the uterus and advised surgery.

The family history was of interest in that her husband had died twenty-five years previously and was said to have had tuberculosis.

The menstrual history revealed a menarche at fifteen years of age with a normal and regular cycle. The menstrual periods ceased eleven years ago without incident except that two years later she had one apparently normal period. She had five pregnancies with normal deliveries.

Physical examination revealed a temperature of 37.6°C. (99.6°F.), pulse of 86 per minute and respirations of 24 per minute. The blood pressure was 124/76. She was poorly nourished, slightly dyspneic and had a distended abdomen. The fundi showed some arteriosclerotic changes. The heart revealed a moderately loud systolic

murmur heard best at the apex. The entire right chest was flat to percussion anteriorly and posteriorly and showed absent tactile fremitus. The breath sounds were absent over the lower half of the right chest and over the upper half they were depressed, high pitched and tubular in character. The left lung field showed no abnormalities. The abdomen was markedly distended and showed bulging of the flanks. There was shifting dullness to percussion and a fluid wave. A large, irregular, firm mass was felt in the lower abdomen which extended a little to the right of the midline and above the umbilicus. Pelvic examination showed a moderate rectocele and the cervix pointing downward and to the right. The mass could be felt with the vaginal finger but it was too large to enable the examiner to make out any details.

Laboratory data included a complete blood count, urinalysis and stool examination which were normal. The Kahn test was negative. Thoracenteses were done on the first (1,300 cc.), second (1,500 cc.), third (2,000 cc.), seventh (1,800 cc.) and thirteenth (1,650 cc.) hospital days. All of these fluids appeared identical in that they showed a small amount of gross blood, specific gravity of 1.014 to 1.018, an average count of 300 cells per cu. mm. (after hemolysis with $\frac{1}{10}$ N HCl acid), with a differential count of 52 per cent mononuclear cells and 48 per cent polymorphonuclear cells on the

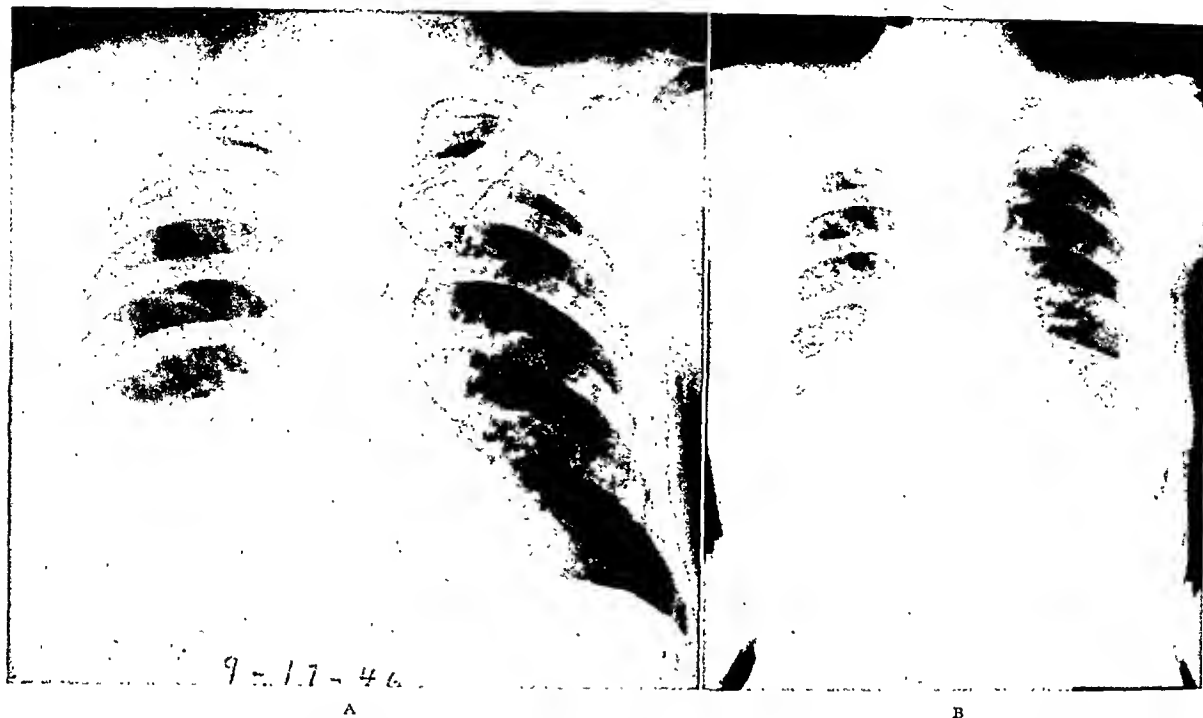


FIG. 2. X-rays of the chest of Case II. A, before the first thoracentesis; B, fourteen weeks postoperatively.

first fluid. The non-protein nitrogen of the fluid was 19 mg. per cent. Microscopic sections of the cellular sediment showed no malignant cells. The blood non-protein nitrogen was 19 mg. per cent and the total protein was 5.4 Gm. per cent with 3.3 Gm. per cent of albumin and 2.1 Gm. per cent of globulin. Fluoroscopy and x-ray of the chest, after the fluid level in the right pleural cavity had been lowered by the introduction of air, showed no abnormalities in the lung fields. (Fig. 2.)

On the eighth hospital day the patient was transferred to the gynecologic service with the diagnosis of Meigs' syndrome. Uterine and ovarian malignancies were considered as possibilities.

On the fourteenth hospital day the patient was operated upon by Dr. William Masters. Caudal anesthesia was used. The entire peritoneal cavity was found to be filled with straw colored fluid. When this was removed, a large, tense, right ovarian cyst was found which measured about 10 by 12 cm. (Fig. 3.) This tumor and the right tube were easily removed. Examination of the remainder of the abdominal cavity revealed no evidences of metastasis or other abnormality.

Recovery of the patient was uneventful. On the sixteenth hospital day (second postoperative day) a right thoracentesis was done but only 10 cc. of straw colored fluid were obtained.

The patient was discharged from the hospital on her twenty-seventh hospital day with diagnoses of (1) Meigs' syndrome; (2) pseudomucinous cystadenoma of the right ovary and (3) right, chronic salpingitis. Six weeks after operation she was again seen at the Washington University Clinics at which time she had gained 10 pounds, felt well, lost her cough but still had a right pleural effusion. Twelve weeks postoperatively she was again examined and the pleural effusion was found to be still present. Therefore, it was planned that she was to be hospitalized again for further study but, at fourteen weeks postoperatively, the fluid had been absorbed, the chest was clear, she felt well and appeared to have completely recovered. (Fig. 2.)

COMMENTS

The first case showed two interesting features: In the first place the abdominal exploration done in 1939 by a capable surgeon failed to reveal any abnormality of the left ovary and yet in four years this benign growth had reached a size of 9 by 10 by 12 cm. and had been associated with effusions into the chest and abdomen. Secondly, the last thoracentesis performed before operation revealed an eosinophilic transudate into the pleural cavity. The

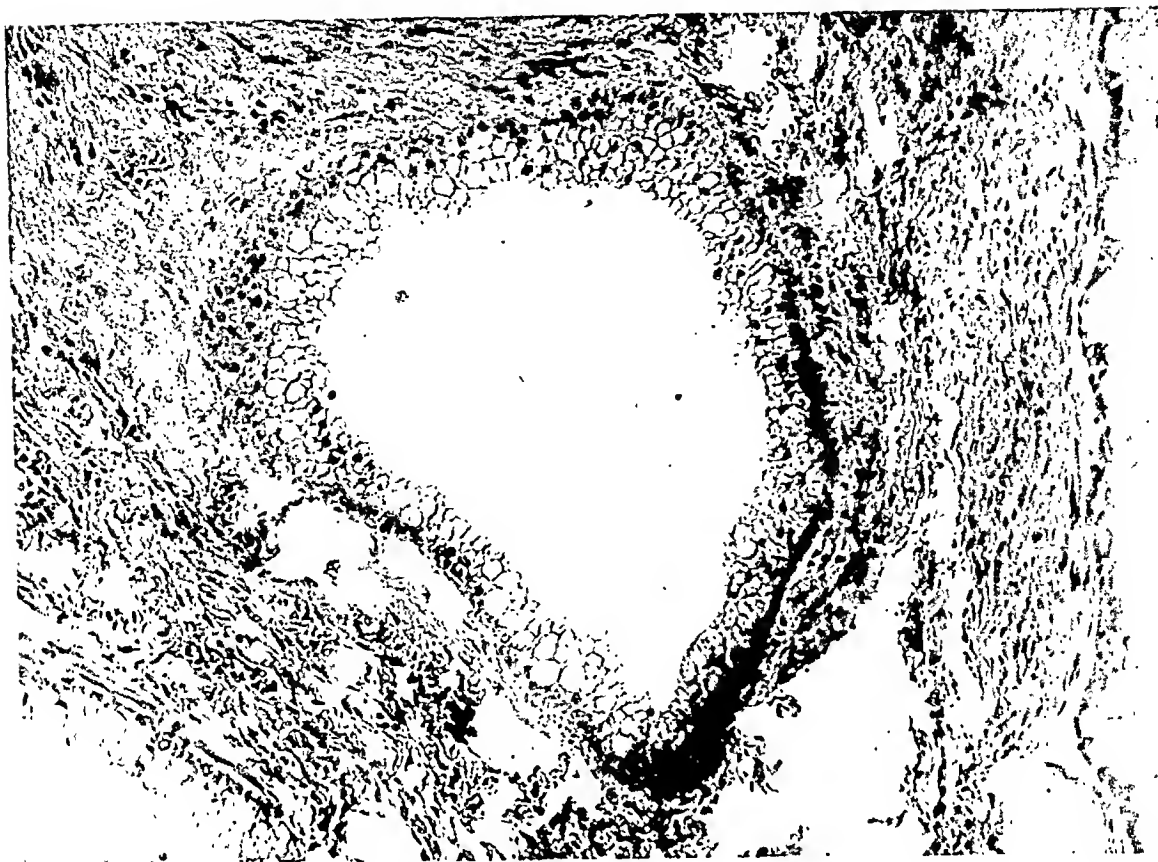


FIG. 3. Photomicrograph of tumor in Case II.

second patient adds another case to those already reported to emphasize that any benign pelvic tumor may give rise to this syndrome.

By far the most interesting problem relating to this syndrome is the pathogenesis of the pleural effusion. Meigs was originally of the opinion that not all fibromas of the ovary are accompanied by ascites and, even fewer, by pleural effusion. In a later paper, however,⁵ he quotes Dr. Thomas S. Cullen who said, "Nearly every case of fibroma of the ovary that I have seen has been accompanied by abdominal fluid," but modifies this statement with his own experience and concludes that about 75 per cent of fibromas of the ovary are accompanied by ascites but, of these, only a few show hydrothorax and that this occurrence is dependent upon circumstances which will be discussed later. At any rate, the occurrence of effusions with this tumor is far too frequent to be coincidental.

In some cases ascites alone is found and

the explanations given are manifold, i.e., inflammation, twists of the pedicle and adhesions to surrounding structures. Rubin, Novak and Squire²⁴ cite an important observation made by Geibel³² which is also quoted in Miller's handbook.³¹ Geibel placed two ovarian tumors in dry containers and in twenty-four hours one tumor secreted one-third of its weight in clear amber fluid. Geibel explained this as being due to extreme cystic dilatation of lymph spaces with ensuing nutritional disorders or necrosis of edematous tissue. In keeping with this observation we think it significant that a great many of the reported cases revealed either frank cysts in an otherwise firm tumor or, at least, microscopic dilatation of the lymph spaces. It is of interest that the photomicrographs of our second case, (Fig. 3) show markedly edematous tissues surrounding the cyst in the section. With regard to fibromas and theca cell tumors, Rubin²⁴ makes the statement, "Considering the fact that the tumor is fibromatous, it is

conceivable that constriction of the afferent lymph or blood vessels takes place in the tumor itself or in its pedicles, and then produces congestion and lymph stasis which may be followed by exudation of tissue fluid on its surface." The reason for the pleural effusion, on the other hand, is more obscure. Many explanations have been suggested; some of them may be easily discarded and others are interesting but so far lack satisfactory proof. They are as follows:

Obstruction of the Azygos Vein. This vein, into which flows the hemiazygos vein from the left side, carries all the blood from the parietal layers of the pleurae and, therefore, might conceivably give rise to pleural effusions if partially or completely blocked. In fact, one patient⁵ was found to have such an obstruction but it is difficult to see how such an obstruction could frequently result from a benign pelvic tumor.

The Alarm Reaction of Selye. Selye²⁷ observed that animals exposed to physical or chemical trauma developed a shock-like state associated with the accumulation of pleural and peritoneal effusions. With continued exposure to the agent, the animals gradually became readjusted and bodily functions approached normal. After three months these animals lost their resistance and succumbed with shock-like symptoms plus accumulation of peritoneal and pleural transudates. Selye, as well as Meigs,⁵ have proposed that the ovarian fibroma itself may act as a noxious agent or perhaps may secrete one which gives rise to the effusions in the chest and abdominal cavities in a manner similar to that observed experimentally by Selye.

Perforations in the Diaphragm. This possibility must be considered since minute perforations between the peritoneal and the pleural cavities have been demonstrated by careful anatomic dissection. Rubin²⁴ states that these minute canals have been demonstrated in both leaves of the diaphragm but are much more numerous on the right; the network of lymph spaces are present throughout the diaphragm except in the

tendinous center portion. Meigs, Armstrong and Hamilton⁵ found a large opening in the diaphragm of one of their patients which communicated with the mediastinum. In this, and others of their cases, India ink was injected into the peritoneal cavity and soon after was found in approximately the same concentration in the mononuclear cells of the pleural fluid. Frequent blood studies following the injection, however, failed to reveal a single instance of carbon particles in the leukocytes of the blood stream. Likewise, the work of Lemon²⁸ has indicated that, in animals at least, some sort of one-way communication may exist between the peritoneal and pleural cavities because he has demonstrated the passing of particulate matter in that direction but was unable to find that such particles passed in the opposite direction. In some cases⁵ air was introduced into one of the body cavities after which the patient was tilted into various positions, but no air could ever be demonstrated to have passed to the other cavity. Likewise, Rubin²⁴ injected kaolin into the abdominal cavity of animals in which he had been able to demonstrate the passage of small India ink and carmine particles from the abdomen to the chest. Following injection of the kaolin, he could no longer show the passage of smaller particles nor the passage of kaolin particles into the chest cavity. These experiments led him to conclude that the pleuroperitoneal canals were very small and would not permit the passage of air and could be blocked by larger particles such as kaolin.

How else then is the pleural transudate to be explained? Fluids from the abdomen and chest of the same patient have repeatedly been shown to be identical as regards their protein content and specific gravity. The typical fluid has been a simple, amber-colored transudate although serosanguineous effusions have been described in about 15 per cent of cases including our second case. Also electrophoretic studies on the fluids have shown identical protein fractions.^{5,24} In only two cases^{12,24} was the pleural fluid different from that found in

the abdomen. The preponderance of the evidence would seem to indicate that the fluid passes from the abdomen into the chest. If this is true, some additional explanations must be made. How is it that patients have complained severely of dyspnea and some have had numerous thoracenteses without any apparent increase in the size of the abdomen or even a sensation of abdominal fullness? How is it, as in our own first patient, that three thoracenteses could be performed in a period of less than a week but yet at operation only 200 cc. to 300 cc. of fluid could be found in the abdomen? Again, how is it that patients with hepatic cirrhosis and with abdomens enormously distended by ascites rarely develop pleural effusion unless on the basis of hypoproteinemia or some other more obvious cause? These are problems which must yet be answered before one assumes that the ascites becomes pleural effusion by the simple expedient of passing through the diaphragm. It is our belief that this may make the problem well worth investigating further. Whatever the method of formation of the pleural fluid may be, it is often rapid since certain of the cases have shown a complete refilling of the chest in twenty-four hours and repeated thoracenteses have been carried to the point of causing dehydration and protein imbalance.

Such obvious explanations as hypoproteinemia, cardiac and renal disease have repeatedly been excluded and no longer are to be considered as causes for the effusions.

We have not been able to explain the suddenly developing eosinophilic pleural effusion in our first case. Unfortunately, there was no differential count of the blood made just prior to the withdrawal of the eosinophilic fluid but previous and subsequent counts failed to show any unusual blood eosinophilia. It has been suggested that this 65 per cent eosinophilia of the pleural fluid developed as an allergic response to the introduction of novocain during thoracenteses. Also, we considered that this might indicate an infection, particularly a tuberculous infection but such

did not seem to be the case. In Loeffler's syndrome, which frequently gives rise to eosinophilic pleural effusions, there is an accompanying allergic pneumonitis but this was not present in our own case. It is of interest that in the case of Gild²¹ the first thoracentesis produced an opalescent fluid with 82 per cent eosinophiles. Two explanations have been offered for the spontaneous eosinophilic effusions: (1) The theory of Ehrlich and Naegeli²⁹⁻³⁰ which holds that there is some chemotactic influence which locally attracts the normal eosinophiles formed in the bone marrow. (2) The theory of Widal and Faure-Beaulieu²⁹⁻³⁰ which is generally adhered to and which holds that the eosinophiles have a local origin in response to some unknown stimulus, and may be formed from any of the leukocytes, hemohistioblasts or from connective tissue cells.

So far as we know there is none other than a coincidental relationship between our case of Meigs' syndrome and the appearance of eosinophiles in the pleural effusion.

SUMMARY

1. Two new cases of Meigs' syndrome are presented and theories as to the pathogenesis of the syndrome are discussed.

2. In one of the cases it is of particular interest that the patient had been operated upon four years previously at which time the left ovary was found to be normal. During the intervening four years the ovary grew to the size of a small grapefruit and was shown at operation to be replaced by a typical fibroma.

3. During the preoperative course of the first patient a right pleural effusion, noted on admission, changed character from that of a simple transudate to a serosanguineous effusion with 65 per cent eosinophiles. No explanation is offered for the change in the nature of the effusion.

4. The second patient had a pseudomucinous cystadenoma of the right ovary with massive ascites and right pleural effusion.

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Metabolic and Inflammatory Histiocytosis^{*}

With Case Reports of Gaucher's Disease, Letterer-Siwe's Disease and Eosinophilic Granuloma†

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THE histiocyte or pyrrole cell or macrophage (Metchnikoff) is a tissue cell of the reticulo-endothelial system which is phagocytic to foreign particles of all sorts. With the lymphocyte it contributes to the repair process which follows the acute phase of a tissue injury. The epithelioid and giant cells of certain inflammatory processes are derived from the histiocytes.

Among the diseases of the histiocytic or reticulo-endothelial system, certain conditions have been grouped as metabolic disorders. These are the lipidoses¹ or lipid histiocytosis, Gaucher's disease, Niemann-Pick's disease and Hand-Schüller-Christian's disease. However, in recent years, Jaffe and Lichtenstein,² Otani and Ehrlich³ and others have described a benign granuloma of bone, now generally called eosinophilic granuloma, with pathological features closely related to Schüller-Christian's disease. It has also been shown that Letterer-Siwe's disease (variously termed aleukemic reticulosis, non-lipoid histiocytosis and reticulo-endotheliosis) bears a strong resemblance to both Schüller-Christian's disease and eosinophilic granuloma. These three conditions are non-familial and show no racial predilection. Histologically, Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma of bone are inflammatory granulomata. There is good reason to believe that they are of infectious origin. The profusion of designations for these conditions has introduced confusion

concerning them. I have thought it proper and useful to discuss and relate these several disorders because these granulomas are not rare and present problems of differential diagnosis. They simulate true neoplasms. They may be confused with myeloma, Ewing's sarcoma, giant cell tumors of bone, metastatic involvement of the spine and tuberculosis. They are not true tumors as they increase in size by the addition of cells and not by cell division.

The essential lipid histiocytoses, Gaucher's and Niemann-Pick's disease, are believed to be inherited metabolic disorders because of their familial occurrence and their predilection for those of the Jewish race. All of our patients with Gaucher's disease were Jewish, one of whom showed a familial incidence.

Schüller-Christian's disease has been considered a storage disease involving cholesterol, the analogue of Gaucher's disease which is a lipid disturbance of the cerebroside kersin and Niemann-Pick's disease, the lipid of which is a phosphatid-lecithin.

With the principal exception of Thannhauser,¹ this view is no longer held. As Mallory⁴ has indicated, Schüller-Christian's disease and, by implication, Letterer-Siwe's disease and eosinophilic granuloma of bone are not "simple so-called storage diseases." The lesions exhibit characteristics of a granulomatous process accompanied by significant grades of inflammatory reaction, both leukocytic and fibrotic. Yet the induction of cholesterol storage by feeding

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cholesterol to rabbits does not result in a granulomatous, inflammatory reaction. It is significant that the spontaneous familial disease of man characterized by cutaneous xanthelasma, hypercholesterolemia and extensive deposits of cholesterol in tendon sheaths and other tissues, i.e., familial xanthomatosis, is not associated with granulomatous reactions and never shows the destructive lesions of bone that characterize Schüller-Christian's, Letterer-Siwe's and eosinophilic granuloma. No familial or racial tendencies have been noted in the latter group of diseases in contrast to the storage group. Biopsy of a fresh lesion shows a granulomatous reaction but little or no lipid deposit. Cholesterolization occurs only with progression of the disease and is secondary and not primary.

It has been suggested,² and this paper will further demonstrate, that there is a close relationship between Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma. The pathologic processes are similar and the clinical manifestations show a considerable degree of overlapping. It would appear that the three entities represent clinical syndromes which are variations of the same basic disorder which might collectively be termed inflammatory histiocytosis.

Our first case illustrates the metabolic disorder, Gaucher's disease. The clinical features of this lipid histiocytosis are hepatosplenomegaly with normal liver function, anemia, leukopenia, thrombocytopenia and a hemorrhagic tendency. There is a familial incidence, pingueculae, which are yellow, wedge-shaped areas at the margins of the cornea, brown pigmentation of the skin and bone lesions which are frequently localized to the lower part of the femur. These characteristics are well illustrated by our first patient.

CASE REPORTS

CASE I. The patient, a thirty-four year old male, was first admitted to the hospital on August 2, 1944. He felt well until November,

1943, when he developed a severe hemorrhage from the gums following a tooth extraction which necessitated two blood transfusions. His white blood count dropped to 1,500. This was attributed to the administration of sulfathiazole. In 1937, he had complained of pain in the right hip for two weeks' duration. An x-ray was taken and he was told that he had Perthes' disease. Examination at the Hammond General Hospital in the army revealed pigmentation of the skin, a greatly enlarged spleen, leukopenia, between 2 to 5,000, with 40 per cent polymorphonuclears. Bleeding time was three minutes and clotting time was twenty-eight minutes. There were 49,000 platelets and there was no clot retraction in twenty-four hours. Bone marrow biopsy revealed characteristic Gaucher cells. Splenectomy was done on February 1, 1944. The spleen weighed 3,960 Gm. Chemical examination of the spleen showed that 50 per cent of this was made up of a glycolipid. Microscopic examination showed characteristic Gaucher's cells throughout the spleen. He was given several blood transfusions and the abnormal hematologic findings improved.

On admission to this hospital, he stated that a half sister had a son with Gaucher's disease. Upon standing he complained of a dull pain in the right hip which radiated down the right leg. Examination at this time revealed a diffuse, brownish pigmentation of the skin. There were no pingueculae. The liver was four finger-breadths below the costal margin and was slightly tender. There was slight atrophy of the right thigh and leg. There was tenderness and a slight protuberance over the right hip. X-ray showed flattening of the head of the right femur. There were numerous cyst-like areas throughout the head. The lower halves of both femurs showed widening of the shaft, thickening of the cortex and the characteristic Erlenmeyer flask appearance. (Fig. 1.) The blood count was 7,800 white blood cells, with 50 per cent polymorphonuclears, 40 per cent lymphocytes, 6 per cent monocytes, 4 per cent eosinophiles. There were 270,000 platelets. Coagulation time was four minutes and bleeding time was one minute. He was furnished with a lift to the right shoe and was discharged. He was readmitted January 11, 1945 because of pain in the left hip of four weeks' duration. The alkaline phosphatase was 30.2, acid phosphatase 5.1 (King-Armstrong units), cholesterol 210, cholesterol esters 162. Cephalin flocculation was negative.

The patient improved with conservative therapy and was discharged February 17, 1945.

Another of our cases of Gaucher's disease, which will be reported elsewhere, is of considerable interest in that the patient developed an osteogenic sarcoma in an area of osteolytic involvement.

Letterer-Siwe's disease is an inflammatory histiocytosis which occurs only rarely beyond the age of two years and usually runs a rapidly fatal course. It is characterized by fever, rash, progressive weakness, enlargement of the spleen and superficial lymph nodes and secondary anemia. There are one or more destructive lesions of the bones. These occur most commonly in the skull with or without lipid deposits. Mottling or honeycombing and emphysema are seen in the lungs. Every grade of transition between Letterer-Siwe's disease and Schüller-Christian's disease is observed, particularly after the age of three or four years when the disease becomes chronic and the picture of Schüller-Christian's disease is more and more frequent. It is emphasized, therefore, that Schüller-Christian's disease is a syndrome characterized by the involvement of the base of the skull and the hypophyseal region by the granulomatous process, producing the characteristic triad of exophthalmos, diabetes insipidus and cystic lesions of the skull. There is a hypercholesterolemia* with secondary lipidization of the histiocytes with cholesterol, producing the characteristic foam cells which are fat-containing histiocytes. It has been indicated, too, that patients with multiple eosinophilic granuloma of bone may develop the Schüller-Christian's syndrome should the base of the skull and hypophyseal region become involved.

Our second case represents an inflammatory histiocytosis predominantly of the Letterer-Siwe's type.

CASE II. The patient, a twenty-one year old white male, was admitted because of progressive

* Thannhauser¹ believes Schüller-Christian's syndrome to be a normocholesteremic xanthomatosis.

weakness of the lower extremities. In 1944, he noted a lump in the right groin which became painful in May, at which time a lymph node was removed and a diagnosis of Hodgkin's disease was made. A subsequent lymph node biopsy, prior to admission here, was reported as Boeck's



FIG. 1. Case 1. Femurs in Gaucher's disease. Note characteristic Erlenmeyer flask appearance of lower halves with widening of the shaft.

sarcoid. He was discharged from the Navy in March, 1945, and then developed swelling and progressive weakness of the right lower extremity associated with pain in the right thigh and knee.

Examination on admission revealed a young white male who appeared poorly nourished and chronically ill. There was a bony defect measuring 2 by 2 cm. in the left posterior parietal region of the skull. There was dullness over the right lower chest and fine râles were heard scattered throughout both lung fields. Lymph nodes were described as egg-sized in the left inguinal region and pea-sized in the cervical chains and both axillae. There was spastic paralysis of the right leg. A fine, pink, maculopapular rash over the lower chest and abdomen was noted. All sputa were negative for tubercle bacilli. Blood calcium was 9.9, phosphorus 4.5. Blood cholesterol varied between 134 to 223.



FIG. 2. Case II. Letterer-Siwe's disease. X-ray of chest showing mottled infiltration and honeycombing.

Acid and alkaline phosphatase were normal. X-ray of the chest showed a mottled infiltration and honeycombing of the upper one-third of the left lung and the paracardiac portion of the



FIG. 3. Case II. X-ray of skull with bony defect involving inner and outer table of left parietal bone.

involving the left parietal bone. The lower half of the right femur revealed cystic, destructive areas with expansion of the shaft. (Figs. 2, 3 and 4.)

Biopsy of an axillary node on September 5, 1945 revealed lipid histiocytosis. Slides received from the U. S. Naval Hospital of tissue taken from the right inguinal region in May, 1944 were interpreted as non-lipoid histiocytosis.

A plaster body-jacket was applied and the patient was given irradiation to the dorsal spine, left parietal region and right femur. The spastic paralysis of the right leg disappeared and the cranial defect diminished in size to 0.5 cm. in diameter. At the time of discharge on August 21, 1946, he was asymptomatic except for mild attacks of unsteadiness of gait. He appeared chronically ill. There were a few shotty lymph nodes in the cervical, axillary and inguinal regions. The chest was emphysematous and there was slight dullness at both apices. No râles were heard. The skin was dry and scaly and had a slight brownish discoloration. The last roentgenogram showed slight progression of the pulmonary infiltration. There was a definite decrease in the parietal defect of the calvarium although new, smaller areas had appeared.

As illustrated in this patient a biopsy of a fresh lesion reveals the granulomatous process but little or no lipid material. Deposition of cholesterol occurs only with progress of the disease. Lipidization takes place with chronicity. The term non-



FIG. 4. Case II. Right femur revealing deformity, cystic lesions and expansion of shaft.

right lung. There was anterior wedging and collapse of the ninth dorsal vertebrae. The bodies of the seventh and the tenth dorsal vertebrae were moth-eaten in appearance. The skull showed a bony defect, 7 cm. in diameter,

lipoid histiocytosis is therefore a misnomer. While the prognosis in the acute cases occurring in infants is poor, in the chronic cases seen in older individuals it is better and our patient appears to be doing fairly well.

Eosinophilic granuloma of bone originally was described as a solitary lesion in 1940. Later Jaffe and Lichtenstein,² Otani and Ehrlich³ and Farber⁵ described multiple involvement of bone with the same histiocytic pathologic entity. Characteristically, there are sheet-like collections of histiocytes some of which show phagocytic activity and among which are prominent numbers of eosinophilic cells, especially eosinophilic leukocytes. There are also fields of hemorrhage and necrosis and numbers of multinuclear giant cells some of which exhibit phagocytic activity. It is seen mainly in children and young adults. Almost any bone may be involved, most frequently those of the vault of the cranium, the ribs, the vertebrae and the long bones, especially the humerus and femur. Symptoms, when they occur, are local. They consist of pain and tenderness at the site of the lesion. There may be a leukocytosis or a slight eosinophilia. The blood cholesterol, cholesterol esters and alkaline phosphatase are usually normal. Roentgenographically, the bone involvement appears as a small or large radiolucent zone. In the calvarium the defects are circular and sharply delineated or punched out. The lesion may show expansion of the cortex and there may be pathologic fractures. The similarity to myeloma, Ewing's tumor and metastatic cancer is emphasized.

The course is benign; the prognosis is good. Treatment consists of small doses of x-ray or curettage. The lesions may resolve spontaneously.

Our third patient is a case of solitary eosinophilic granuloma of bone.

CASE III. The patient, a twenty-six year old veteran, was admitted October 23, 1945. In August, 1945, he began to complain of severe pain in the left side of his head.



FIG. 5. Case III. Solitary eosinophilic granuloma of bone. Note sharply defined area of cystic bone destruction in left parietal bone.

Examination disclosed an area of softening of the skull in the left temporoparietal region, approximately 2 cm. in diameter. It was somewhat tender. Neurologic examination was normal. The remainder of the physical examination was negative.

X-ray examination of the skull revealed a 2 cm. in diameter, circular area of cystic bone destruction, sharply defined, in the left parietal region. This was surrounded by a faint, poorly defined zone of increased bone density. Both the outer and inner tables showed evidence of bone destruction. (Fig. 5.) The dorsolumbar spine, pelvis, chest, humeri and feet showed no abnormalities. The blood cholesterol was 286. Acid phosphatase was 3.0 and alkaline phosphatase 7.4 (King-Armstrong units). Operation showed a sharply defined, circular tumor in the left parietal bone near its prominence which was soft and grayish-yellow in color. This had destroyed the entire thickness of the table. Only the overlying periosteum was present.

Histologic examination showed a large number of eosinophiles. There were also histiocytes present, some of which were multinucleated and some of the histiocytes contained eosinophilic pigment. Most of the eosinophiles were of the multinuclear variety although an occasional one was of the mononuclear type. The diagnosis was eosinophilic granuloma of bone.

Following administration of 1,500 roentgens (in air) to the lesion, the patient showed considerable symptomatic improvement. His headaches disappeared. There was no evidence noted



FIG. 6. Case iv. Multiple eosinophilic granuloma of bone. Cystic areas in distal portion of femur and proximal portion of tibia and fibula.

of regression of the skull defect, but there was blurring of the margins and the appearance of a thin outline of bone 2 mm. in width. The patient was afebrile throughout his stay. He was discharged December 12, 1945.

It has been emphasized in the literature²⁻⁵ that eosinophilic granuloma of bone, as the name implies, is limited to the skeleton. Indeed, cases with visceral involvement have not been reported to my knowledge.^{6*} The last patient, illustrating multiple eosinophilic granuloma of bone and also pulmonary infiltration presumably by the granulomatous process, is therefore of special interest. It also substantiates the essential identity of the three manifestations of inflammatory histiocytosis under discussion since visceral involvement is characteristic of Letterer-Siwe's disease and Schüller-Christian's disease. It will be recalled that our second patient with atypical Letterer-Siwe's disease exhibited the characteristic

honeycombing or mottled involvement of the lungs.

CASE IV. A twenty-two year old white male was admitted on February 27, 1946. The patient was in fairly good health until November 14, 1944, when he entered an army hospital because of trench feet. On December 22, 1944, in the Dental Clinic, a cyst of the mandible was found. Prior to going overseas he had the two lower incisors extracted because they were loose in their sockets. The sockets never seemed to heal. Early in February, 1945, he noted pain in both thighs which was intermittent in character and lasted only several minutes at a time. There was tenderness of the thighs. Blood count on one occasion revealed 4 per cent eosinophiles. Biopsy of the right clavicle was reported as eosinophilic granuloma and was confirmed by the Army Institute of Pathology. The patient received a total of 10,200 roentgens through nine ports. Following this, he improved greatly. The bony defect disappeared, his appetite improved and he acquired more strength. In August, 1945, he had an evening fever which was unexplained and thought to be due to his disease. Final diagnoses were eosinophilic granuloma involving the skull, mandible, right clavicle, right and left radii and right and left femora.

On examination at this hospital, the patient appeared thin, somewhat undernourished and was ambulatory. The lower jaw was edentulous. There was a defect of the middle two-thirds of each mandible. A circular postoperative scar was present over the right clavicle. There was no lymphadenopathy. The chest was negative. Blood pressure was 104/70. The liver and spleen were not palpable. There was tenderness over the proximal portion of the right tibia. There was no swelling or depression. There was a defect over the middle two-thirds of the anterior surface of the right clavicle.

X-rays showed numerous punched out, clearly defined areas of decreased density over both frontal and occipital bones. The right forearm showed oval shaped areas of decreased density measuring 2.0 cm. in greatest diameter in the proximal one-third of the radius. Several areas of decreased density were noted in the mid-portion of the shaft of the left humerus, the distal portions of both femurs and proximal portion of the tibias. (Fig. 6.) Several areas of decreased density were noted in the upper one-third of the radius and ulna. The chest showed that the lung markings were exaggerated

* Since submission of this paper for publication, a case of eosinophilic granuloma of bone with multiple lesions of bone and pulmonary infiltration has been reported.⁷

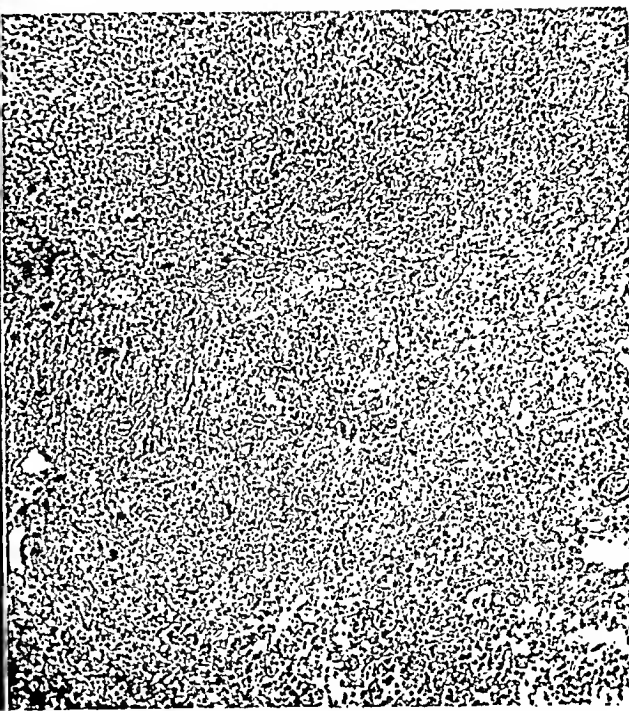
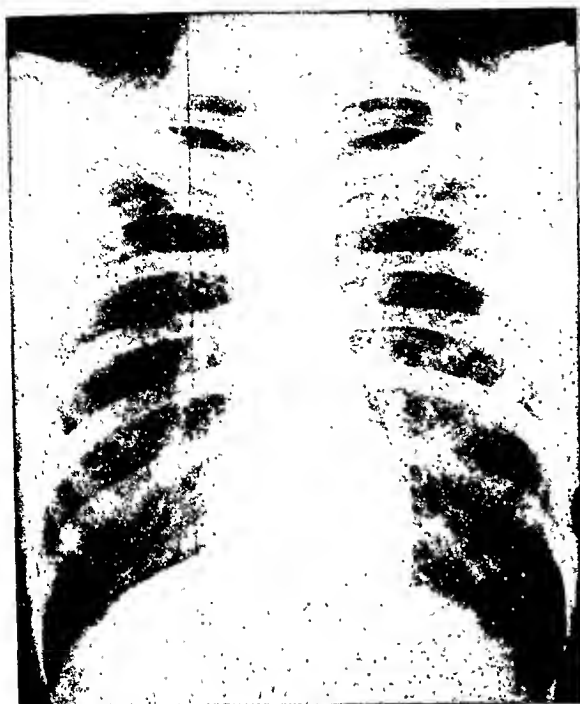


FIG. 7. Case iv. Fine mottled infiltrations involving both lung fields.

FIG. 8. Case iv. Section from left tibia seen under low power. The light-staining cells are histiocytes. The dark-staining cells are eosinophils. Note the presence of giant cells.

due to fine infiltrations occupying the entire left lung and the upper two-thirds of the right lung. X-ray findings were interpreted as changes in bones and lungs due to lipid granulomatosis. (Fig. 7.)

The alkaline and acid phosphatase were 4.8 and 2.4. Sedimentation index was 17. Calcium and phosphorus, urea nitrogen and blood sugar were normal. Blood count was normal. There were 1 per cent eosinophils present. There was no Bence-Jones protein in the urine. Biopsy from the upper third of the left tibia was reported as eosinophilic granuloma. (Fig. 8.)

The patient was given radiotherapy and was discharged on July 4, 1946 asymptomatic and in good condition.

CONCLUSIONS

It appears clear that eosinophilic granuloma of bone and its congeners, Hand-Schüller-Christian's disease and Letterer-Siwe's disease, represent merging clinical variations of an essentially similar pathologic process, best described collectively by the term inflammatory histiocytosis. These syndromes or entities are believed to be due to some obscure infectious process and produce a secondary disorder of the lipid metab-

olism. They are to be clearly differentiated from the primary lipid metabolic disorders, Gaucher's and Niemann-Pick's diseases. Knowledge of these conditions will obviate confusion with malignant tumors involving bone and other granulomas such as tuberculosis and syphilis.

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Cor Pulmonale*

Observations on Forty-two Autopsied Patients

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COR pulmonale constitutes one of the less common types of heart disease. Although recognized as a distinct entity, there is some difference of opinion as to the rôle played by chronic lung disease in its etiology.

The older concept was that the narrowing and thrombosis of pulmonary capillaries in emphysema elevated the blood pressure in the pulmonary circuit and thus put a strain on the right ventricle, which underwent dilatation and hypertrophy, and finally failed. Certain studies carried out in the past twenty years seemed to indicate that chronic lung disease does not produce cor pulmonale; but investigations of the last ten years herald a return to the older theory that chronic lung disease plays a definite part in its etiology.

Kountz and Alexander have followed this change in view, at first rejecting a connection between chronic lung disease and cor pulmonale, and later returning to the older viewpoint. In 1927 Alexander, Luten and Kountz¹ said "As a rule the heart remains free from injury after continuous bronchial asthma despite the attendant emphysema." In 1929 Kountz, Alexander and Dowell² wrote "It is believed that despite peripheral signs which simulate cardiac decompensation, advanced emphysema does not necessarily affect the heart." In 1934 Kountz and Alexander³ presented experimental evidence showing that emphysema alone does not cause hypertrophy of the right heart, but in 1936 Kountz, Alexander and Prinzmetal⁴ came to somewhat different conclusions. They maintained that the heart is affected in the majority of patients with emphysema and

that there is experimental evidence that right ventricular dilatation and hypertrophy occur chiefly in the earlier phases of emphysema rather than in the later stages.

Other workers question a relationship between cor pulmonale and chronic lung disease. White and Brenner⁵ said "Ordinarily, asthma, emphysema and pulmonary tuberculosis, even though of high degree, do not produce cor pulmonale." In 1936 Rubin⁶ stated that in the absence of associated cardiovascular disease a selective or preponderant enlargement of the right ventricle in emphysema is an uncommon finding. In 1937 Parkinson and Hoyle⁷ said "Cardiac failure from emphysema alone is surprisingly rare."

More recent work refutes this. For example, Griggs, Coggin and Evans⁸ concluded that chronic pulmonary disease is an important cause of cor pulmonale. They found that right ventricular hypertrophy occurred in 54 per cent of patients with pneumoconiosis without other pulmonary or cardiac disease. They found that right ventricular hypertrophy occurred in 29 per cent of the patients with emphysema. Parker⁹ found that in a high percentage of cases emphysema leads to ultimate failure of the heart. He also concluded that the severity of emphysema was closely related to the extent of right ventricular enlargement. Scott and Garvin¹⁰ stated that the right ventricle is burdened in emphysema, presumably by an elevation in pulmonary pressure, and that it undergoes dilatation and hypertrophy and ultimately fails. Hallock and Rigler¹¹ concluded that chronic pulmonary disease is an important cause of cor pulmonale and subsequent heart failure.

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Schiller, Colmes and Davis¹² stated that cor pulmonale due to chronic bronchial asthma is a more common disorder than is generally recognized. In discussing their series of cases of cor pulmonale, Spain and Handler¹³ concluded that diffuse obstruc-

tive emphysema was the underlying significant pulmonary factor in the vast majority of cases. In the light of the conflicting conclusions just mentioned, it would seem that further study of this subject is indicated.

This paper deals with observations on

TABLE I
CASES OF COR PULMONALE

Comparative Data	Spatt and Grayzel	Spain and Handler ¹³	Scott and Garvin ¹⁰
Number autopsied cases	42	60	50
Criterion for diagnosis	Right ventricular wall averaging 5 mm. or more in thickness	same	same
Sex	32 males (76%) 10 females (24%)	56 males (93%) 4 females (7%)	48 males (96%) 2 females (4%)
Peak age incidence	51-70 yr.	50-65 yr.	Majority over 50 yr. of age
Peak incidence of heart weight	300-450 Gm. Average weight 401 Gm.	Average weight 460 Gm.*	400-500 Gm.
Thickness of right ventricular wall	36 cases (86%) 5-8 mm. 5 cases (12%) 9-11 mm. 1 case (2%) 20 mm. Average 7 mm.	Average thickness of right ventricular wall 8 mm. with extremes of 6 and 14 mm.†	41 cases (82%) 5-8 mm. 3 cases (5%) 10 mm. 2 cases (3%) 9 mm. 2 cases (3%) 12 mm. 1 case (2%) 11 mm. 1 case (2%) 14 mm.
Associated pulmonary disease	Emphysema, 29 cases; bronchiectasis and lung abscesses, 7 cases; pulmonary tuberculosis, 3 cases; carcinomatosis, 2 cases; pulmonary arteriolar sclerosis, 1 case	Emphysema, 40 cases; bronchiectasis, 6 cases; bronchial asthma, 6 cases; silicotuberculosis, 3 cases; pulmonary tuberculosis, 2 cases; kyphoscoliosis, 1 case; pulmonary arteriolar sclerosis, 1 case; organized pulmonary thrombi, 1 case	Emphysema, 32 cases; emphysema with conglomerate silicosis, 7 cases; emphysema with ulcerative tuberculosis, 5 cases; emphysema with fibroid tuberculosis, 1 case; emphysema with silicotuberculosis, 1 case; conglomerate silicosis, 1 case; pulmonary fibrosis, 1 case
Symptoms	Exertional dyspnea, cough and cyanosis in most patients over a long period of time; venous distention, hepatomegaly, edema, and ascites less frequent and of shorter duration	Most patients complained of dyspnea suddenly getting worse; also, hemoptysis and cyanosis; later they had engorged veins, hepatomegaly, edema and increased venous pressure	Cough, exertional dyspnea and cyanosis were usual long-standing complaints; venous distention, hepatomegaly, edema and ascites rarely lasted longer than 6 to 8 mo.
Red blood cell count	Of 23 cases, when red blood count was available, 9 cases (39%) had a count of over 5,000,000; the highest was 7,560,000	Extremes of red blood cell count 3,300,000 to 6,500,000; average count, 4,960,000†	In 21 of 32 cases (66%) the red cell count was more than 5,000,000; the highest was 7,900,000

* Only average weight reported in this instance.

† Only average and extremes of thickness recorded.

‡ Percentage of cases with over 5,000,000 red cell count not recorded.

forty-two cases of cor pulmonale collected from the autopsy records of the Jewish Hospital of Brooklyn. These cases were chosen after elimination of all instances with valvular disease of the heart, those with more than minimal coronary sclerosis,

TABLE II	
Disease	No. of Cases
Emphysema.....	29
Bronchiectasis and lung abscess.....	7
Pulmonary tuberculosis.....	3
Carcinoma with lymphangitic spread (carcinomatosis).....	2
Pulmonary arteriolar sclerosis (marked)	1

those with clinical hypertension and all congenital lesions and luetic cardiovascular disease. (Table I.)

It is recognized by various workers in the field that the best postmortem criterion for diagnosis of cor pulmonale is the separate weight of each ventricle. However, this information is rarely obtained. The authors have adopted the next best criterion, that used by other workers in the field,^{8,10,13,14} a right ventricular wall averaging 5 mm. or more in thickness.

Of the forty-two cases observed, thirty-two (76 per cent) were males and ten (24 per cent) were females. The average age at time of death in the series was fifty-eight years; in the males sixty years and in the females fifty-three years. The largest group of patients (twenty-five cases) were between fifty-one and seventy years of age.

The weight of the hearts in the females varied from 250 to 340 Gm. and averaged 300 Gm. In the males they varied from 300 to 600 Gm. and averaged 401 Gm. Sixty-five per cent of the hearts weighed between 300 and 450 Gm. (twenty-seven cases).

In thirty-six cases (85.7 per cent) the thickness of the right ventricular wall varied between 5 and 8 mm. In five cases (11.9 per cent) the right ventricular wall varied between 9 and 11 mm; in one case (2.3 per cent) it was 20 mm. thick. Varying grades of left ventricular hypertrophy were seen. In ten cases (24 per cent) the left ventricular wall averaged 15 mm. or over in thickness. There was no strict correlation between the thickness of the two ventricles.

All the patients had some form of chronic lung disease, as seen in Table II.

Many of the patients with emphysema showed accompanying changes such as bronchiectasis, mild pulmonary artery sclerosis, fibrosis of the lungs and pleural adhesions. In two cases of emphysema there were marked degrees of kyphoscoliosis.

Of thirty patients in whom complete clinical histories were available, twenty-five complained of exertional dyspnea and of these, twenty noted this symptom for many years. Of these thirty patients, nineteen complained of chronic cough, with or without expectoration, over a long period of time. Cyanosis was slightly less frequent; it was present in seventeen cases. Edema, ascites, distention of neck veins, hepatomegaly and precordial distress were of much shorter duration than the former group of symptoms. Eight of these thirty patients had a history of bronchial asthma for periods varying from seven to fifty years, averaging twenty-six years.

Many of the patients in this series died shortly after entering the hospital so that no laboratory data are available except in twenty-three cases. In those patients in whom a red blood count was recorded nine (39 per cent) had a red cell count of over 5,000,000; the highest was 7,560,000.

COMMENTS

The conflicting opinions on various phases of cor pulmonale expressed by different workers may be due to the different criteria used in diagnosing cor pulmonale, and also to the fact that no attempt has been made to evaluate the variations in the dimensions and weight of the heart relative to body size, weight and sex.

The mechanism of dilatation and hypertrophy of the right ventricle seems fairly generally agreed upon. The pulmonary changes destroy and narrow blood capillaries in the lungs, causing pulmonary hypertension, which in turn increases the strain on the right heart thus resulting in dilatation and hypertrophy.

There are different explanations for the

accompanying left ventricular hypertrophy in some cases. Some workers believe that the anatomic relationship of the two ventricles is so intimate that hypertrophy of one chamber ultimately involves the other. Others believe that the accompanying left ventricular hypertrophy is due to the anoxemia which occurs in cor pulmonale. Still others maintain that the cause of left ventricular hypertrophy is as yet undetermined. The authors believe that both factors mentioned above contribute to left ventricular hypertrophy.

CONCLUSIONS

The data collected in this series of cases support the theory that chronic pulmonary disease plays an important rôle in the etiology of cor pulmonale.

Cor pulmonale is much more common in males than in females. Death in cor pulmonale occurs most frequently between the ages of fifty-one to seventy. At death the average age of the females in our series was seven years less than in the males.

Long-standing symptoms of exertional dyspnea, cough and cyanosis (indications of pulmonary disease) evidently reflect the first stage of the process. These are frequently followed by distention of the neck veins, hepatomegaly, edema, ascites and precordial distress (indications of the heart disease). The latter symptoms of heart involvement are of much shorter duration than the indications of pulmonary disease.

In over one-third of the patients (39 per cent) the red blood cell count was over 5,000,000.

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Urinary Calculi*

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THE past five years have brought forth new theories, new data and new technical methods for the treatment of urinary calculi. A review of the subject is presented herein.

COMPOSITION OF URINARY CALCULI

Calcium oxalate. This stone is by far the most common in this climate on the diet prevalent in the United States. It forms in neutral urine or in urines which are slightly alkaline or acid.

Calcium phosphate. This stone is often mixed with both magnesium and carbonate complexes and is the next most common stone; it forms in alkaline urine.

Uric acid. This stone forms in acid urine and is to be found in heavy meat eaters.

Cystine. This stone also forms in an acid medium; it is often familial and is sex-linked to the females. We have several families of cystine stone formers in which many members of the family have cystine stones.

Most stones are not pure but mixtures of the first three mentioned, with one compound or the other predominating. Oxalate stones are commonly small, dark, rough and hard. Calcium phosphate stones tend to be soft, whitish and chalky, often forming casts of the infected calyces or pelves in which they lie. Uric acid stones are usually small and may be of any color although classically they are golden yellow. Cystine stones are commonly staghorn shaped and have a waxy, almost translucent character. Most staghorn calculi are either calcium phosphate or, in rare cases, cystine.

A new development in calculus analysis is the application of geologic crystallographic methods of analysis to these stones. A well trained geologist after some practice can

make an excellent estimate of the amount of each compound present in the stone.¹ The trouble with this method is that technicians cannot readily be trained in this art.

THEORIES OF STONE FORMATION

All stones start as a small nucleus. If this nucleus is exposed to an overconcentration of any of the urinary salts mentioned above, it will grow rapidly into a stone. A good deal is known about the causes and prevention of the hyperconcentrations of urinary salts that make for stones but it is not yet known why the nucleus forms in the first place. It is well known that urine contains a far greater concentration of crystalloids than could possibly be dissolved in any ordinary aqueous solution. Crystals are present in most urine samples yet the bulk of the crystalloids does not precipitate out about these crystals. This is, as yet, a poorly understood colloidal phenomenon which is under investigation by physical chemists and may be far more important in the explanation of the formation of calculi than any of the more mechanical factors which we will consider here.

Some of the newer concepts of the initiation of the nuclei of stones postulate pre-calculus lesions in the form of (1) calcium plaques which form on the renal papillae,² caused perhaps by the action of distant toxins or by local necrosis³ or by phagocytized calcium from the convoluted renal tubules. Many substances are concentrated in the convoluted tubules where Mayo Clinic investigators⁴ found small amounts of calcium in phagocytes which they postulate may be carried down to the region of the pelvic epithelium to form deposits which erode through to the pelvic wall.

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Randall has found many such lesions in large series of autopsies. (2) Inspissated crystalline plugs in the terminal collecting tubules are frequently seen in autopsied kidneys. This phenomenon is seen with sulfa drugs when a plug of crystals protrudes from the terminal collecting tubule onto the surface of the renal pyramid. (3) Lesions of the tubular epithelium involving tubular cell death and postmortem calcification, the cells then sloughing to form a nidus for a stone. We also see this sort of thing in sulfa drug damage to the kidneys when damaged epithelial cells in the walls of the tubules die and may become calcified.³ When and if such precalculus lesions form as nuclei on the pelvic wall, they are adherent to the wall of the kidney, not lying free. Later, they may break off in the renal pelvis. It is well known that trauma plus infection will cause stones in the kidney⁵ and Rosenow claims that infection alone may cause stone formation, especially if organisms from stone formers are used. If, in experimental animals, the infected kidney is damaged by a cauterizing electrode, a stone will form at once. Foreign bodies or ulcerations in the bladder will cause stones to form, perhaps due to differences in surface tension in the urinary tract, the epithelium normally being protected by its own coatings.

Figure 1 shows a bougie which was left in the bladder and became the center of a very large calculus.

The older concepts of a nidus of desquamated epithelium, of bacteria or of pus are looked upon with increasing doubt since such phenomena occur in non-stone formers all the time. Furthermore, such niduses have not been demonstrated by investigators who made serial sections of many stones. It is not known why foreign bodies become calcified in some people and not in others or why only segments of the foreign bodies become calcified.

Once the nucleus is formed any factor which increases the excretion of urinary salts will cause the stone to grow rapidly. The factors which increase the concentra-



FIG. 1. A large bladder stone which formed around a foreign body (bougie) inserted into the bladder during an attempted abortion.

tion of salts in the urine should be looked for in stone patients, since they may be corrected. They are as follows:

1. Stasis, which may be due to obstruction by the prostate gland, strictures of the urethra, ureteroceles, strictures of the ureteropelvic junctions or calyceal neck obstructions. These obstructions may be corrected surgically.

2. Bed immobilization, as in body casts or in chronic illnesses, will cause osteoporosis with hypercalcinuria which reaches its peak about a month after bed rest is started. These patients drink too little water if left to their own devices. An output of over 2,000 cc. a day must be maintained.

3. Infection of any kind in the urine will aid and abet calculus formation and if urea-splitting organisms such as *Bacillus proteus* or some of the staphylococci are present large quantities of ammonia are formed. The urine becomes strongly alkaline and is loaded with calcium salts.

4. Concentration of the urine, as by inadequate fluid intake or by excessive sweating. The Army Air Forces did a fine study of this aspect of the problem and found it most important in the formation of calculi in its members during the war.⁶ The Air Force also conducted an excellent study on

the effect of warm climates and sweating upon calculus formation. They found that in the European Theater the incidence of kidney stones among the troops was 0.5 per thousand per year whereas in the warm climate of the China, Burma, India Theater and the Pacific Theater the incidence was 2.5 per thousand per year. In all areas where sweating was heavy, stone formation was prevalent. The flying personnel had a much greater incidence of calculi than the non-flying personnel. This was attributed to the fact that flyers were nervous, perspiring considerably as a result, and were often clothed in heavy flying clothing and flak suits during the take-off at warm, low levels during which time they perspired further. In addition, there was very little drinking water in aircraft which were on long trips and fluid intake was low. The type of diet did not influence the incidence of stones but did influence the type of stone which was formed. For instance, the flyers who partook heavily of iced tea, chocolate and greens formed oxalate stones whereas in the Navy the men formed uric acid stones because of their high meat diet.

5. Conditions which cause a hyperexcretion of calcium in the urine are: (1) Hyperparathyroidism. (2) Eating of large quantities of dairy products causes a transient hyperexcretion of calcium in some normal people and a pronounced unexplained hyperexcretion in most stone formers.⁷ (3) Sippy regimens are to be avoided in known calculus-forming patients. (4) Large doses of vitamin D will cause a temporary hyperexcretion of calcium in the urine. (5) Long immobilization, as in fracture patients who are in body casts or in chronically bedridden patients who develop osteoporosis with hyperexcretion of calcium. (6) Marked vitamin A deficiencies appear to cause heavy phosphaturia and a persistently alkaline urine, in addition to epithelial ulcerations which rapidly become infected and encrusted. This work has been confirmed in experimental animals, not in the human.

6. Cystinuria is a familial disease in which the urine is loaded with cystine. This

tendency seems to be sex-linked to the female. Hyperexcretion of xanthine is another such disease. These calculi form in acid urine but again calculi do not form in all patients with such hyperconcentration, only in 2 or 3 per cent of these patients. The cause of the origination of these stones is not known.

All of the lesions which we have described can be recognized and corrected. However, for every patient with a lesion that can be corrected there will be several others in whom nothing can be found to account for their being stone formers or to explain the aggravation of any incidental stones which they might have. There are, of course, known stone belts in the world. Florida and California, Central Russia, Indo-China and Syria are well known as stone districts, whether due to the hot climate or to certain peculiarities in the diet of the natives is not known. It is not related to the "hardness" of the drinking water or to geologic strata. In South Africa, for instance, an analysis of some 11,000 white patient admissions showed an incidence of 5 per cent renal calculi whereas a group of 1,000,000 negroes, living in the same area, showed no calculi at all. It was suggested that the negro diet was somewhat richer in vitamin A.⁵ Certainly stones are more common among the cereal-eating groups of the world population.

SYMPTOMS

The classical symptoms of urinary calculi are attributed to three factors (1) Local trauma to the pelvis or ureteral wall by sharp spicules of stone which causes severe intermittent spasm or bleeding, and later erosion of the wall with infection and further bleeding. (2) Obstruction of the ureter. If this is acute, there is colic; if it is gradual, there is no pain as in the slow occlusion of the ureter by carcinoma. Both blockages lead to hydronephrosis. (3) Infection. The kidney is very vascular and the damming back of infected urine readily leads to septicemia with chills and fever. Admission

temperatures on the urologic service often run as high as 105°F.

Figure 2 shows a small stone less than 1 cm. in diameter which has fallen from the kidney down into the mid-ureter. This small stone blocked the ureter causing renal colic and extreme discomfort. Huge staghorn calculi which are much larger than this stone may cause no symptoms at all in the kidney. They lie silently in the kidney but erode the wall of the pelvis causing infection and frequency of urination with burning. It has been said that the kidney is an inarticulate organ but that the bladder speaks for it.⁹

DIAGNOSIS

Diagnosis of renal stones is not difficult. A history of urinary frequency, discomfort or hematuria is easily elicited. The pain distribution is suggestive, the urine is readily analyzed and x-rays show the stone. It is up to the doctor to make this diagnosis. Many plain films of the abdomen taken in emergency wards are technically poor and will not show small stones due to poor preparation of the patient, to feces or gas, or to hurried technic. Some 5 to 10 per cent of all stones are not opaque to the x-ray as in the case of the occasional pure uric acid stone.

If there is doubt about the plain x-ray, 20 cc. of diodrast is injected into the patient's vein and pictures are taken. Hydro-nephrosis and hydro-ureter may be caused by a stone which is so small and has so little density that it will not show in the initial x-rays.

A cystoscopic catheter will, of course, verify the existence, location and size of a suspected stone. An air pyelogram can be used for non-opaque stones. Good x-ray technic has made the wax-tipped bougie almost obsolete.

The differential diagnosis between urinary calculus and appendicitis or pelvic inflammatory disease is sometimes difficult because of the similar pain distribution. Rarely, cholecystitis may be confused with kidney disease. Cystoscopic and x-ray ex-

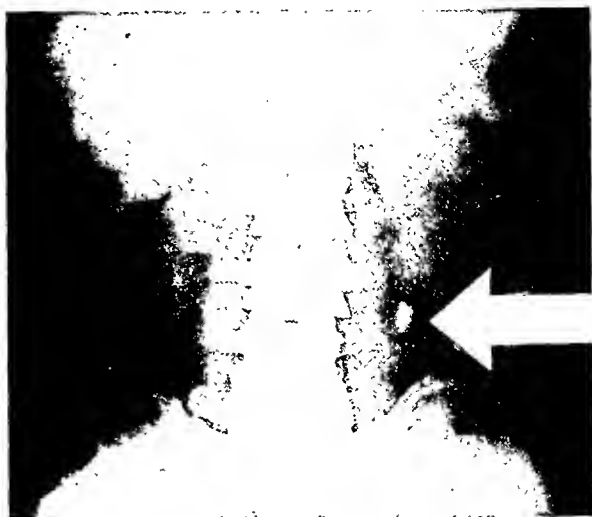


FIG. 2. A small stone which blocked the left mid-ureter causing severe colic.

aminations will establish the diagnosis. Nevertheless, three fourths of the patients with right ureteral stones come to the hospital with a scar in the right lower quadrant, an indication that all too often an innocent appendix had been removed.

TREATMENT

If there is colic, morphine sulfate gr. $\frac{1}{4}$ (0.016 Gm.) and atropine gr. $\frac{1}{100}$ (0.6 mg.) are given. If this does not relieve the colic in one hour, the dose is repeated. For the second medication papaverine may be given intravenously in a dose of .03 Gm. to relax the ureter.

Strain the urine. The patient is instructed to urinate into a vessel through four thicknesses of gauze. The probable appearance of the stone is explained to him in detail. He is told to expect a hard fragment of the size indicated by the x-ray. It may be any color, black, white or yellow and it may be broken up into sand. It will never be as large as the patient anticipates. If this is not said, patients have a tendency to discard small stones as not measuring up to their expectations.

A culture is taken of the urine since infection is a prominent feature in these cases and chemotherapy will obscure any later cultures.

The patient's intake and output are measured and a blood urea nitrogen is

taken. One must be always on the alert for a calculus anuria wherein calculi on one side will, in an unexplained manner, cause the shut-down of both kidneys which may be most refractory to treatment. There have been four such patients in this hospital in the past fifteen years, three of whom died.

Urinalysis is ordered to include microscopic examination and a stained smear of the urinary sediment. A test with Sulko-
witch reagent for excessive calcium excretion¹⁰ should be done.

Chemotherapy appropriate for the organism found in the urine is started. Penicillin may be given up to 50,000 units every three hours intramuscularly; streptomycin up to $\frac{1}{4}$ Gm. every three hours for periods up to three weeks and sulfadiazine may be given if there is no blockage of the urinary tract. Sulfacetamide is particularly good in these cases in that no urinary alkalization is required for this more soluble drug.

A serum calcium, phosphorus and alkaline phosphatase should be taken in every patient with stones and repeated at intervals to rule out hyperparathyroidism.

Antispasmodic Drugs. Depropanex, a pancreatic extract, has not helped our patients. Syntropan and trasentin appear to have some usefulness and a new drug called amethone is presented¹¹ as being particularly useful in renal colic. Actually, few of these drugs have served us as well as morphine and atropine. If high fever and pain persist, a cystoscopic catheter is passed up beyond the stone to provide drainage. After such a catheter has been in place for one or two days and the edema and infection have subsided the catheter may be removed and often the stone will pass within the next two or three days.

Cystoscopic Manipulation. The newer cystoscopes are considerably smaller than the caliber of the normal urethra and have a surprisingly large visual field inside the bladder. Small stones in the lower ureter may be removed (1) by introducing catheters into the ureter around the stone, after which the stone will pass, or (2) by introducing a stone-removing basket, a device

of fine wires or catheters which are bowed out in such a manner that the little stones may fall in between the wires and thus be removed when the basket is withdrawn¹² and (3) by means of small rubber bags on the end of ureteral catheters which may be introduced up to the stone and the bags dilated to a caliber larger than the stone. Then, as the bag is withdrawn down the ureter beneath the stone, the stone may follow the bag out into the bladder.¹³ Usually, small stones under 1 cm. in diameter will pass spontaneously, but they may take as long as two or three months and meanwhile infection and erosion of the ureter will occur. If stones are present in the bladder and have grown to a size of 2 cm., they will not pass through the urethra but can be broken up with a lithotrite, an instrument for crushing stones which are in the bladder. The operation of crushing stones this way is referred to as litholapaxy.

If the patient's stone is not amenable to any of these methods and is doing damage, it should be removed surgically. The approach to renal and upper ureteral stones is through the flank; for ureteral stones lodged below the brim of the pelvis the approach is through a para-inguinal or paramedian incision and for bladder stones the approach is suprapubic, down through the space of Retzius and into the bladder. All of these approaches are extraperitoneal. In removing multiple small kidney stones it is often difficult to locate all of the tiny fragments in the tips of calyces. Some of these are frequently left behind and then form the nuclei for new stones. A new technical development which is helpful in these instances is the fibrinogen-thrombin coagulum which has been worked out at Duke University¹⁴ for injection into the exposed renal pelvis at operation. After four minutes this coagulum becomes twenty times as tough as an ordinary clot, and after it has solidified a larger incision is made in the pelvis and the coagulum is withdrawn, carrying with it the tiniest stones which might otherwise have been left behind. At this writing the coagulum is not yet on the commercial market.



FIG. 3. Left renal calculi before irrigation with Suby's stone-dissolving solution introduced through a nephrostomy tube.



FIG. 4. The same patient after twenty days of irrigation. Suby's solution caused the stones to crumble and they were lifted out through the nephrostomy opening.

Stone-dissolving Solutions. The current status of stone-dissolving solutions is developmental. They are citric acid solutions which have been buffered with magnesium oxide and bicarbonate to make them less irritating. They can be used on the occasional large, soft, calcium phosphate stones. They are also useful against alkaline-encrusted cystitis lesions in the bladder. They are useless against the more frequent hard stones, such as the calcium oxalate kidney stones or the usual hard bladder stones. The chief drawbacks to their use are the difficulties in application of the solution to the stones. A tube must be maintained in the kidney for periods up to three weeks in order that the stones can be continually washed with the solution. A tube must be kept either in the ureter or in through the flank for this period. If the stones do not loosen or crumble within three weeks, the interior of the kidney may become irritated by these strong solutions. The solutions are being developed further by Dr.

Fuller Albright, Dr. Suby and their group in Boston.¹⁵ Rarely do these solutions dissolve a stone completely although now and then a spectacular result is obtained.

Suby's solution was helpful in the following case: Figure 3 is the x-ray of a patient who was irrigated through a nephrostomy tube. It is apparent that at the end of twenty days (Fig. 4) all of his large laminated calculi were gone. These stones, however, did not dissolve but merely became loosened and softened to such an extent that they fell into the nephrostomy tract and could be grasped with a Kelly clamp. Suby's solution is often used in tidal drainage apparatus for paraplegic patients to prevent bladder concretion.

Can stones be dissolved by diet? Yes, they can be, but very rarely. Cystine stones, if pure, will sometimes dissolve in a strongly alkaline urine after many weeks. It has been argued by Higgins⁵ that many alkaline stones will dissolve on an acid-ash diet. However, acid-ash diets may, in truth, cause

an increase in the amount of calcium available in the urine for stone formation. They are relatively ineffectual in lowering the pH of the urine, especially in the presence of infection. It is so much easier for the patient to take ammonium chloride or nitrate that acid-ash diets are being used less and less. The ease with which these medications can throw a patient with damaged kidneys into acidosis must be kept in mind.

PREVENTION OF RECURRENCES

Dilution of the urine is first on the list of preventive measures. All stone patients are instructed to drink 3 quarts of water daily. If the patient is a paraplegic or is bedridden with a fracture, the intake is raised to over 4 quarts per day. A diet is prescribed which is low in the elements from which the stone was formed. In addition, transitory showers of hyperexcretion of these elements must be prevented. For instance, patients who have had stones which contained calcium are cautioned not to drink large quantities of milk or fruit juice at any single meal. Instead, they should take small amounts at long intervals.

Obstructions in the urinary tract are removed. Ureteropelvic junctions are carefully studied for obstructions that can be corrected and renal ptosis is remedied if it is severe. Ureteroceles are opened and bladder neck obstructions or strictures are removed.

Urinary tract infection which is so often present is now attacked vigorously according to the organism found upon culture. Streptomycin and penicillin are given in adequate doses. Sulfacetamide is particularly useful because of its ready solubility but leukopenia and anemia must be guarded against. Mixed chemotherapy is becoming increasingly versatile and effective and when it is combined with improved drainage much can be accomplished.

The patient's blood calcium and phosphorus are checked repeatedly since early in the disease only low phosphorus may be found. It must be borne in mind that if hyperparathyroid patients develop renal damage, as they so often do, they may go

into uremia; whereupon the blood phosphorus will rise and the blood calcium will come down, sometimes to relatively normal values. It is therefore important that the blood urea nitrogen be determined in all these patients. Parathyroid tumors are removed if they are present. A high calcium intake given after parathyroidectomy in order to replace the bone damage may cause renal calculi to reform unless precautions are taken. The urine must be kept very dilute and clear of infection and obstruction.

To prevent stasis in patients who are immobilized in bed or in casts for long periods of time, change their position frequently, force fluids and keep their urine clear and acid. All stone patients are x-rayed at one, two, three, six and twelve months after they have passed the stone. If the patients have had uric acid stones, they are kept on an alkaline-ash diet at least for a time; although if we assume that precalculus lesions are present, even in uric acid stone-forming patients, we might merely change the character of the stone from an acid stone to an alkaline stone. If the blood uric acid is high, measures should be taken to keep the urine roughly neutral in reaction. If the patient is suspected of having a vitamin A deficiency, a photometric test is made. It is probably advisable to give vitamin A to all stone-forming patients in view of the present incompleteness of our knowledge as to the formation of stones even though this factor seems to be somewhat over-rated. Usually 100,000 units of vitamin A per day are prescribed. It is occasionally possible for a patient to bring to the laboratory some calculi which have been passed by other members of his family. These should be analyzed with an eye to possible familial factors such as cystinuria.

New research is currently under way which may make it easier to prevent certain stones from forming. It is known that the body maintains its calcium in the urine in solution partly through the elaboration of citric acid in the urine. It is also known that the administration of estrogenic hor-

mones will increase the citric acid output. It was therefore suggested by Dr. Shorr¹⁶ of New York Hospital that if one were to administer estrogens and at the same time administer aluminum hydroxide preparations in large doses (up to 160 cc. a day) in order to lower the excretion of phosphorus in the urine, one might hope to prevent further stones from forming in people who are known to form phosphate stones readily. No large series of cases on these regimens has been reported but two obstacles have already appeared. First, ordinary aluminum hydroxide preparations tend to make for constipation in these patients and may even cause intestinal obstruction. Magnesium trisilicate is now added to amphojel to counteract the constipation. Second, it has been revealed that other experimenters¹⁷ use estrogens to cause stones in male rats and although they attribute the stone formation to stasis in the urinary tract, due to hypertrophy of the prostate and other tissues in male rats, this has nonetheless discouraged use of estrogens.

In 1937 a Danish worker, Hammersten,¹⁸ suggested that a high magnesium intake was beneficial in the prevention of stones and might even bring about stone dissolution, at least in animals. This work is under investigation by Barrett.¹⁹

It is this type of research which is in progress today from which we hope to learn more and more practical methods for controlling calculus disease.

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Seminars on Protein Hydrolysates

Problems in the Evaluation of Protein Therapy^{*}

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EVALUATION of the protein nutritional status is becoming increasingly important in medical and surgical practice. In spite of the availability of several excellent reviews^{1,2} on the subject a number of misconceptions still prevail. A false feeling of security may result from erroneous conclusions drawn from fragmentary evidence. An anticipated response to a given type of protein therapy may not occur when special conditions interfere with normal protein metabolism.

In this paper an attempt will be made to review and to scrutinize the various factors to be considered in the evaluation of data relating to protein nutrition, and to analyze a number of peculiar situations that challenge the classical concepts of protein metabolism and, in practice, present pitfalls in the evaluation of protein therapy.

GENERAL CONCEPTS

Evaluation of the Protein Nutritional Status. The only tissue "biopsied" for evaluation of the protein nutritional status of the body is blood plasma. The assumption is often made that the concentration of plasma protein reflects the protein concentration of the body in general. That this is true in the dog has been shown by Weech³ who demonstrated that the loss of tissue protein of the dog subjected to chronic protein depletion is paralleled by a loss of circulating albumin at a rate of 1 Gm. of albumin for 30 Gm. of tissue protein. One may assume that this relationship holds true in man in those rare instances in which one deals with

simple protein starvation in the presence of adequate hydration. In most types of human hypoproteinemia, however, it is unlikely that the loss of circulating protein correctly reflects the general protein nutritional status. In instances of acute loss through hemorrhage or in burns this relationship does not prevail and relatively small amounts of plasma protein given intravenously may replete the protein deficit. In other special situations the total protein deficit may be considerably greater than would appear from the concentration of plasma protein.

The plasma protein concentration is affected by many variable factors which do not change the total circulating protein. Simple physical factors, such as changes in the patient's position, will alter the plasma volume. Hemoconcentration or hemodilution resulting from changes in the state of hydration of the patient may likewise rapidly alter the plasma volume and thereby change the plasma protein concentration.

For these reasons the practical value of the plasma protein determination is questionable in the majority of cases. There are chemical, methodological considerations which further impair the value of "total protein" that so often determines the clinician's decisions.

It has been found by Adams⁴ that the falling drop method in copper sulfate as described by Phillips⁵ and associates for the determination of plasma proteins, while fairly reliable within the normal range, is not accurate enough in the hypoproteinemic range. This same relationship has

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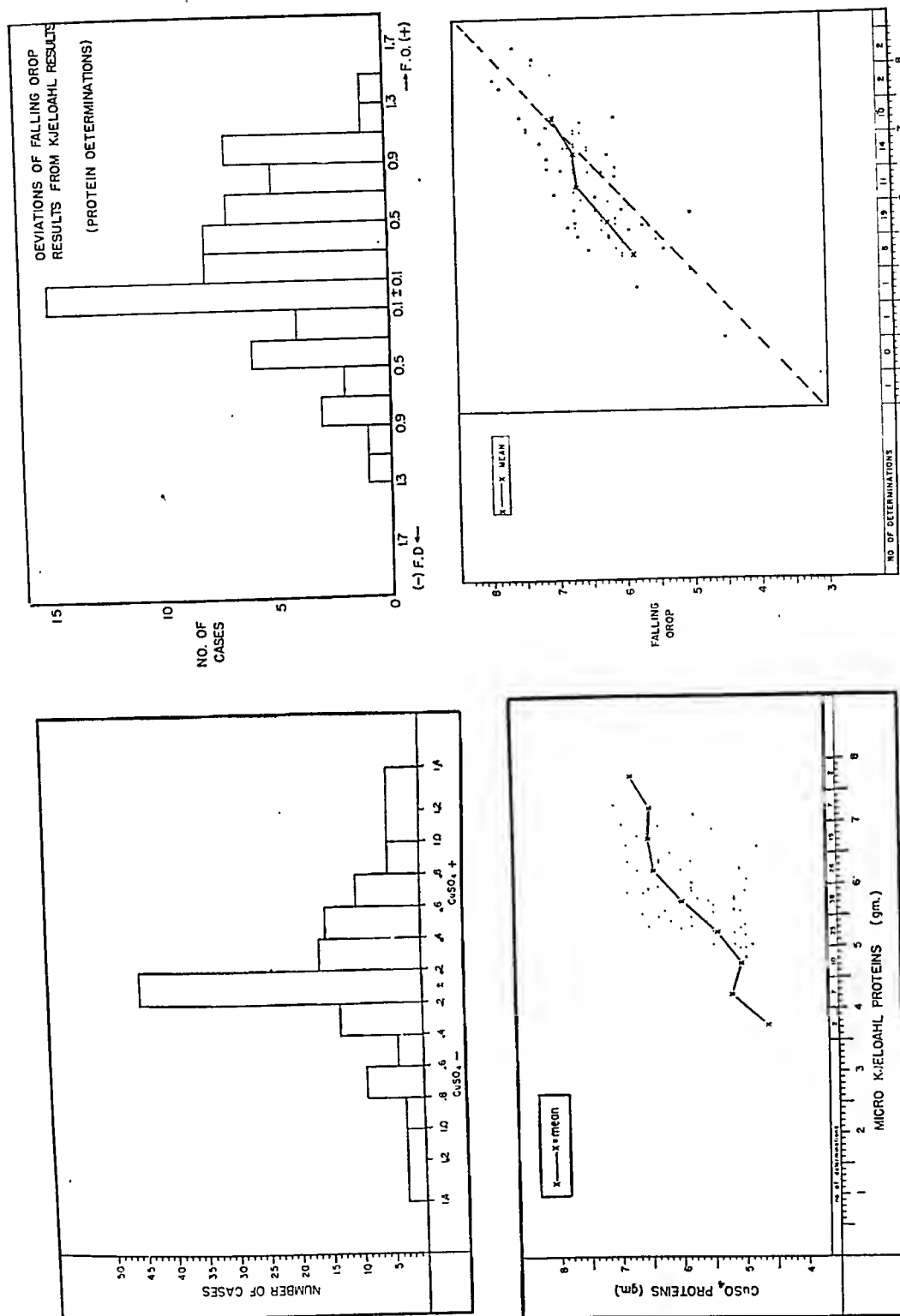


Fig. 1. Comparison between values of plasma protein concentration obtained by the Kjeldahl method and by methods making use of measurements of specific gravity (Phillips⁵ on the left, Kagan⁶ on the right). The charts on the left are reproduced from the paper by Adams et al.⁴ (Through the courtesy of the *J. Lab. & Clin. Med.*, 31: 507-513, 1946.)

been encountered by other authors* (Fig. 1) in comparing the falling drop method of Kagan⁶ with the values obtained for total proteins by the Kjeldahl method. For the present, only the Kjeldahl method as a measure of the nitrogen (corrected by the values obtained for non-protein nitrogen) will give an accurate estimation of plasma protein concentration. The methods most frequently employed by clinical laboratories for the rapid determination of the concentration of plasma proteins are intrinsically unsatisfactory in the range where they are most important for the evaluation of the patient's plasma protein concentration.

In addition to the total protein concentration one has to consider that various protein components may be selectively lowered or elevated. The use of a single figure to express the ratio of albumin to globulin is to be condemned as misleading and the values for each of these proteins should always be considered separately.²

Accurate determination of the plasma albumin concentration by salting out methods presents considerable difficulties. The most reproducible definition of plasma protein components today is by electrophoretic methods which separate the components by their specific mobility in an electric field. The salting out method of Howe⁷ determines the "sodium sulfate soluble" albumin. This corresponds to the albumin and $\alpha_1 + \alpha_2$ globulin of the electrophoretic analysis. Salting out at different concentrations⁸ may result in better duplication of the electrophoretic pattern. Provided the fractions obtained by the various salting out procedures are always the same, these methods are probably satisfactory.

It has been found by Petermann et al.⁹ that under certain circumstances the "sodium sulfate soluble" albumin consists of more α_1 and α_2 globulin than ordinarily. Thus in patients with gastric cancer, for instance, the administration of a high protein diet may alter the solubility of α_1 and α_2 globulin in such a way as to make them

* Unpublished observations by Trunnell, J. B. and Homburger, F. shown in Figure 1.

more likely to appear as "albumin" in the Howe method. The "albumin" as measured by this latter method will increase and will create the impression that the therapy is effective, whereas actually, as shown by electrophoresis, the true albumin value may

TABLE I
COMPARISON OF ANALYTICAL RESULTS OF HUMAN ALBUMIN IN SERA CONTAINING DIFFERENT AMOUNTS OF ELECTROPHORETIC ALBUMIN, WHICH IS TAKEN AS 100 PER CENT*

Albumin in Sera, Per Cent	Per Cent of Electrophoretic Albumin Found by		
	Precipitin Reaction	Salt Fractionation	Alcohol Precipitation
20-30	101 \pm 4.0	195 \pm 1.0	
30-40	102 \pm 3.6	144 \pm 5.2	135 \pm 3.4
40-50	105 \pm 2.7	142 \pm 3.8	121 \pm 3.6
50-60	106 \pm 3.8	133 \pm 1.9	120 \pm 4.7

* From Chow, Homburger, DeBasc and Petermann.¹²

remain unchanged in the absence of any response to the therapy used. Alcohol precipitation in the cold¹⁰ has been difficult to control and has not been reliable in our hands. A new method measuring the precipitate in serum formed by the addition of an animal antiserum prepared by immunizing the donor animal with human albumin has produced results in the hands of its author, Dr. B. F. Chow,^{11,12} that compare favorably with electrophoretic results obtained in our laboratory on the same samples. (Table I.)

It may thus be hoped that simpler and more reliable methods will become available for the measurement of the albumin fraction of blood proteins.

SPECIAL CONSIDERATIONS

There are peculiar disturbances of protein metabolism which render the evaluation of the protein nutritional status even more difficult than it usually is. These may be classified into two groups.

Instances with High or Normal Plasma Protein in Spite of Tissue Depletion. The plasma protein concentration may show an ap-

parent increase due to dehydration with a reduction of plasma volume. This situation occurs in surgical patients and in a number of conditions involving profuse sweating,

ensuing hemoconcentration may mask a reduction of the total circulating protein.

Instances of Low Plasma Proteins Persisting at Hypoproteinemic Levels in Spite of Repletion

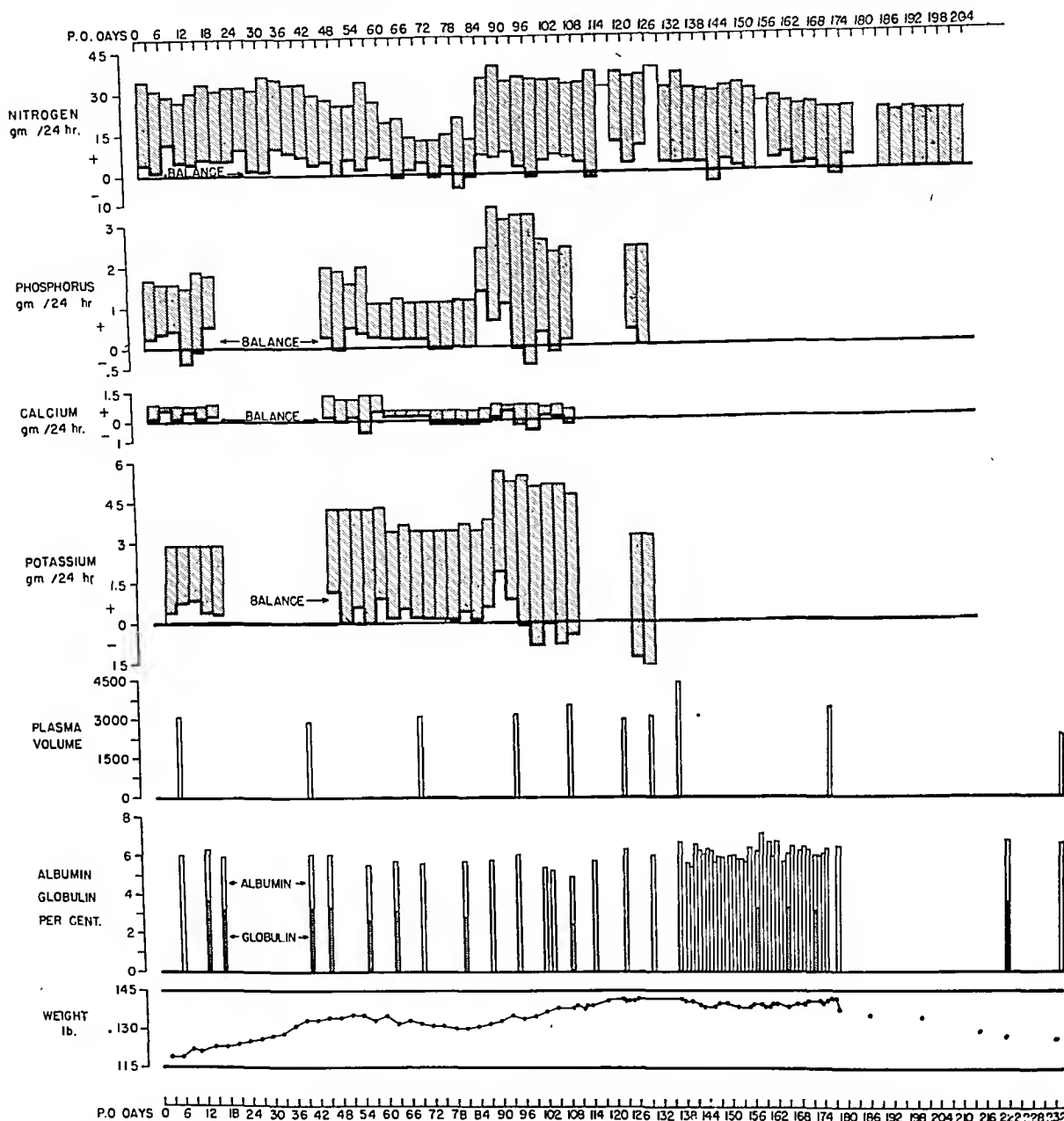


FIG. 2. Study of protein regeneration. Case M. H., No. 83958, S. K. 116. Balance study in a patient with gastric cancer. Note retention of nitrogen, phosphorus, potassium and calcium and weight increase lasting more than 150 days. Increase of circulating plasma protein occurs late and is only temporary, decreasing again with weight loss and reduction of plasma volume as tumor recurs. Patient died thirty-three weeks after study was completed.

elevated temperatures and/or prolonged diarrhea and vomiting. In cases of edema with fluid shifts into the extravascular space the reduction of the plasma volume and the

of Tissue Proteins. There are some disorders of protein metabolism which are characterized by a hypoproteinemia persistent in spite of a high protein intake with evidence

of protein regeneration in tissues other than blood. This has been described in certain types of kidney disease by Keutmann and Bassett¹³ and in tuberculosis by Co Tui.¹⁴

In Figure 2 is shown a nitrogen balance study and electrophoretic analysis of plasma

carcinoma, such as weight loss and weakness, thirty-three weeks before the patient's death from extensive abdominal carcinomatosis. It may be argued that the depletion of protein was so extreme in this case that unusually large amounts of protein were

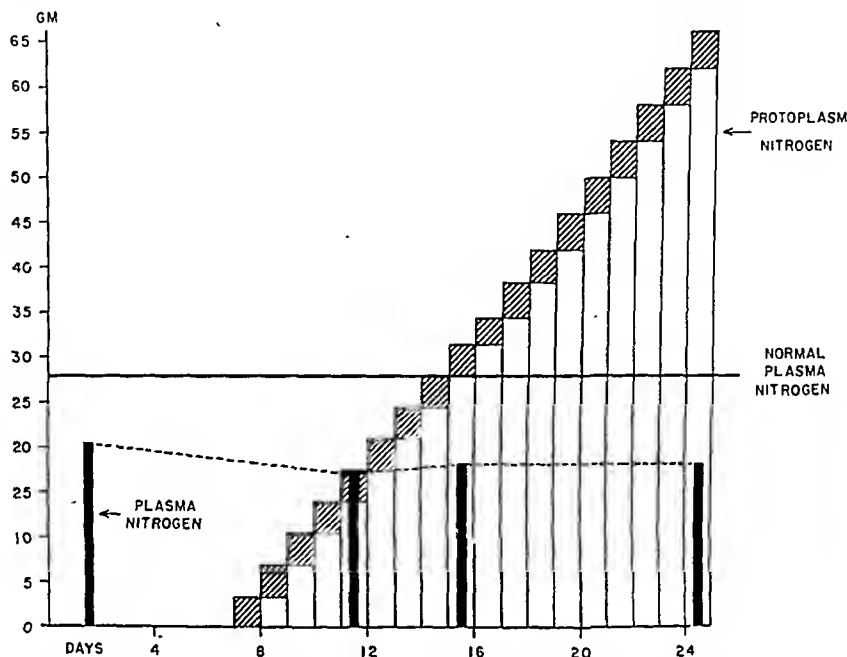


FIG. 3. Estimated protein distribution in a patient with familial idiopathic dysproteinemia.¹⁵ Nitrogen retained during eighteen days' balance study (cross-hatched areas) is not utilized to increase plasma protein which has remained low while the patient remained on high protein intake during one year preceding this study.

proteins together with studies on the plasma volume in a case of cancer of the stomach. In this case the patient had undergone partial gastrectomy eleven days before the study and died of recurrent carcinomatosis seven months after the study. It may be seen that fair amounts of nitrogen, potassium, calcium and phosphorus were retained throughout the long period of investigation. Yet no regeneration of plasma protein was observed and the albumin values remained exceedingly low throughout the study. There was a continuous weight gain that levelled out toward the end of the study when apparently the individual's general protein nutritional status became stabilized. After seven months of a high protein diet, regeneration of plasma protein finally took place. Curiously, this occurred at a time when there were signs of recurrence of the

necessary to make up the loss and that plasma protein regeneration finally occurred as the general deficit was made up; but this seems unlikely in view of the clinical history indicating plasma protein repletion at the time of recurrent weight loss.

In another case hypoproteinemia persisted for two years while the patient had a protein intake of at least 100 Gm. and maximally 200 Gm. per day without evidence of nitrogen loss in urine and feces. This situation prevailed in a case of idiopathic dysproteinemia.¹⁵ The nitrogen distribution in this case is shown in Figure 3 during a period of nitrogen balance study carried on for eighteen days at the end of the first year of this patient's high protein intake. Again it is clear that in spite of nitrogen retention (accompanied by phos-

phorus and potassium retention) no regeneration of plasma protein occurred.

Finally, the postoperative phase in major surgical procedures presents a situation in which the condition of apparent eu- or hyperproteinemia may be seen caused by hemoconcentration and in which, conversely, intractable hypoproteinemia may also be encountered. The pathogenesis of the latter condition in such instances is entirely different from that prevailing in gastric cancer, idiopathic dysproteinemia, etc. It is the excessive nitrogen loss which in such examples of "alarm reaction" renders replacement of lost protein difficult. With forced protein feeding, using hydrolysates by mouth, jejunal tube and/or parenterally, positive nitrogen balance^{16,17,18} and protein regeneration¹⁹ can usually be obtained.

To achieve this at least 0.6 Gm. of nitrogen per Kg. of body weight per day has to be given. Plasma administration may be the only effective way to restore normal plasma protein levels rapidly until the general protein deficit has been corrected.

COMMENT

It has been shown that for various reasons evaluation of the protein nutritional status of a patient is exceedingly difficult and that the reliance placed on clinical methods is justified only to some extent in uncomplicated malnutrition. In many types of protein depletion measurements of the concentrations of total plasma protein, albumin and globulin give information which is not only incomplete but may actually be misleading, since the results may indicate success of protein therapy when in reality the state of depletion is not materially altered by the measures employed.

There are ways to improve the value of these methods and to approach the problem in a more rational fashion. Estimation of plasma volume simultaneously with protein concentration is an improvement and the technics^{20,21} are relatively simple provided conditions are well controlled. A Kjeldahl

method for nitrogen determinations, even though cumbersome, should be used whenever possible for the determination of plasma protein. Nitrogen balance and water balance studies, of course, provide the most complete information. Obviously, such investigations cannot be carried out in daily practice.

For adequate evaluation of the protein nutritional status and of the patient's progress under protein therapy the following procedures are suggested: (1) daily weighing under similar conditions; (2) records of fluid intake and output; (3) records of total nitrogen intake; (4) determination of hematocrit and (5) plasma protein concentration determination by a Kjeldahl method.

Daily weighing is possible in most patients with the present methods of early ambulation and relatively simple procedures enable one accurately to weigh patients in bed. In many types of malnutrition the weight alone will serve as an excellent guide for the evaluation of therapy provided there is no edema.

Knowledge of the patient's *fluid balance* gives an excellent measure of his state of hydration and once this has become stabilized a fair estimate of the plasma volume can be made on the basis of body weight accepting the assumption that the plasma volume is 5 per cent of body weight.²² These considerations hold only in the absence of ascites or edema. Even in the presence of edema, however, the simple procedures of weighing the patient and following his fluid intake and output will provide valuable information on the state of nutrition and hydration.

A *record of the total nitrogen intake* is particularly helpful in the postoperative phase and should be kept whenever protein therapy is being administered. It is surprising how low in protein are some of the regimens used routinely in many institutions for postoperative nutrition. The simple order left by the physician that a high protein diet be given is not sufficient as

the actual intake is often far below the desired levels.

The simple procedure of *determining the hematocrit value* in a Wintrobe tube can provide information on many factors such as sedimentation rate, hemoglobin concentration and red cell volume, icterus index and plasma volume. This is a most valuable adjunct for evaluation of the protein nutritional status and is not used often enough.

In the light of the data available from the above procedures the figures obtained for *protein concentration of blood plasma* gain an altogether different significance than when they are used alone and a fair estimate of the patient's protein nutritional status becomes possible.

As to the determination of albumin and globulin concentration it is our impression that this best be omitted unless electrophoretic or immunologic methods are available. For purposes of following the response of a patient to nutritional therapy the determination of albumin by the Howe method may be more misleading than helpful.

Using the methods described for the evaluation of the protein nutritional status of patients, one will find various types of hypoproteinemia as described earlier: (1) hypoproteinemia without general tissue depletion that will be readily and permanently correctible by plasma infusions, or by blood transfusions if complicated by anemia; (2) hypoproteinemia with general tissue depletion which will respond to massive and prolonged oral protein therapy unless there are factors interfering with protein absorption or digestion (malnutrition, chronic loss from wounds, gastrointestinal lesions other than cancer, etc.); in the postoperative phase, types 1 and 2 are often combined; (3) hypoproteinemia that will persist in spite of tissue protein repletion, such as in gastric cancer, tuberculosis, certain types of renal disease, idiopathic hypo- and dysproteinemias. In these instances both high oral protein intake and administration of plasma by vein will be necessary. (4) Finally, hypoproteinemia

obscured by hemoconcentration but the other criteria will show that there is tissue depletion and restoration of normal hydration will reveal the true degree of hypoproteinemia.

SUMMARY

Pitfalls and shortcomings of some of the methods used to evaluate the protein nutritional state are discussed. Some peculiar situations have been described in which evaluation of protein nutrition is particularly complicated and in which the response to protein therapy is unusual.

Methods for better evaluation of the protein nutritional state are suggested, permitting the classification of various types of hypoproteinemia into groups requiring different types of protein therapy.

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Clinic on Psychosomatic Problems

A Case of Hysteria

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Psychiatric Service of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr. Foundation.

DR. RICHMOND HOLDER: The patient (M. G. H. No. 292026), a twenty-five year old married woman, entered the hospital complaining of numbness and weakness of the left leg of six months' duration, together with pains in the left groin and rectum. She dated the onset of her illness to a hemorrhoidectomy thirteen months before. While recovering from this operation, she had several "convulsions" manifested by twitching of the face, choking respirations and uncontrolled writhing in bed. She herself could remember nothing of these spells.

Rectal complaints persisted despite dilations and a second operation was performed. Following the latter, sharp pains occurred in the left groin which soon radiated down the left leg. The patient lost her appetite and gradually her weight declined. Nine months before admission she had a severe spell of weeping and trembling.

Six months prior to admission the pain became constant and generalized over the entire left lower extremity. The patient was treated by several physicians and finally had a spinal manipulation under pentothal anesthesia. From that day on there was complete numbness of the leg.

The patient was admitted to another hospital for diagnostic work-up; lumbar puncture and pantopaque myelogram revealed no abnormalities. A presumptive diagnosis of hysteria was made and she was referred to the Massachusetts General Hospital for psychotherapy.

The past medical history included tonsillectomy at the age of four years and the usual childhood diseases. There were no early neurotic traits except nail biting. Five years before the present illness there

had been an acute episode of abdominal pain, nausea and vomiting. Exploratory laparotomy revealed a normal appendix. An aberrant renal artery was found and ligated but this was not believed responsible for the symptoms.

The patient was the only child of an unknown father and a delinquent mother. She was adopted when she was four years old by a strict, middle-aged, childless Scotch couple and was never told anything about her real parents. She recalled being teased about this by her playmates, and also remembered that when she was unruly her foster parents would reproach her with the fact that she was adopted. Her foster mother was a cold, exacting woman whom the patient resented, but she was very fond of her foster father and could confide in him.

She finished high school without difficulty and apparently made an adequate social adjustment. In her sophomore year at college she had a "nervous breakdown" and had to quit. At first the details of this illness were not obtained as the patient could not remember what had happened. Later it came to light that she had been unhappy at college because her foster mother interfered with her personal affairs and gave her an inadequate allowance although the family was well off financially. One day the patient was found lying unconscious on the floor of her room and after a brief period of hospitalization she was sent home. No organic cause for the episode was found.

She then began nurses' training but quit to be married after a brief courtship at the age of twenty-one. She was always frigid though she did not find intercourse unpleasant. There were two uncomplicated

pregnancies and both children were healthy. The patient's husband, since discharge from the Army, had found himself stuck in an unsatisfactory job and had been drinking quite heavily.

Upon physical examination the pronounced limp was noteworthy. Dragging her left foot, the patient walked with a wide base and yet was able to support her entire weight upon the left leg. This extremity was cooler than the right and slightly cyanotic. The deep reflexes were bilaterally equal and brisk. There was anesthesia of the left lower extremity and loss of vibratory and position sense from the inguinal ligament down. Voluntary muscle strength of the left leg was diminished but there was no atrophy. The remainder of the physical examination revealed no further abnormalities.

Laboratory data, including urinalysis, complete blood count, Hinton test, chest x-ray and basal metabolic rate were normal. The electroencephalogram was considered a borderline record by reason of occasional slow waves, but there was no evidence of a dysrhythmic focus.

Psychotherapeutic interviews were then begun. The patient at first related her attitude toward her mother-in-law who resented the patient's higher social status and made remarks about her parents being stingy. A good deal of hostility was evident and she was encouraged to speak of it freely. (One usually finds that negative feelings are more easily expressed toward a person with whom the patient does not have a strong emotional tie.) She then told that she had married to get away from the strictness of the foster home. While her husband was in the Army, she had lived with his mother and sister-in-law. Her younger baby was a few months old at the time, adding to her burden, and the household was in a continual state of tension and unexpressed ill-will. (It is interesting that her rectal pain became worse at this time and the first operation was done.)

Because her relationship with her adopted parents seemed important in various incidents, the interviews were then directed

toward that general topic. Soon it was noted that she talked mostly about her stepfather, and so the focus was narrowed to her feelings and attitudes toward him. She told how he always took her part in family quarrels which made her feel better. Then one day, with tremendous emotional feeling and tears, she poured out a flood of information. Shortly before her first operation the father was found to have a carcinoma of the prostate. During the next few months he rapidly became worse. His legs were weak, he walked with difficulty, and the last time she had seen him before her back manipulation he had been walking with a cane. (From that time on she herself could not walk without a cane.) The psychiatrist at this point kept his own activity to a minimum, merely encouraging the patient to talk and gently directing her toward the topics which seemed most emotionally charged. No interpretations were made.

In the next interview she again wept as she told of her shock at the realization of her father's impending death. For a long time she could not admit it to herself. She said: "I can remember saying to myself, 'Why couldn't it be me? I've disappointed him . . . made a poor marriage and got into a terrible family. If I lose my father, I've lost that good part of my life . . . the others don't mean anything to me.' Last night I realized his symptoms were so like mine and I wanted to take them on myself. I feel terribly guilty. I want to make myself suffer. It's too late to make it up to him now. I never cried about it before. I always put it out of my mind."

At the end of this interview she threw down her cane, saying: "I don't need this to walk with any more," and limped out of the room unaided. On the following day sensory examination of the leg was normal and the lividity had disappeared.

When presented at the Staff Conference, the patient walked into the room easily with only a trace of a limp. She was cheerful and pleased with her improvement and stated that her leg was almost as good as ever.

DISCUSSION

DR. STANLEY COBB: This is more satisfactory than if we had used amytal narco-synthesis and I believe more permanent than if we had gone right ahead and used suggestion. We have rid her of the symptom by insight therapy and that is excellent. We will have on our hands a woman who had a monosymptomatic hysteria, who is in difficulties with her husband, and in a social situation that does not sound easy to help. From now on shall we use more psychotherapy of this sort? It is obvious that she needs more social service in trying to arrange her life. She should get out of those five rooms; she will soon be upset by the loss of her father.

DR. HOLDER: Her foster father will live from three to nine months. When he dies the financial situation will improve because he has set up a trust fund. The husband now has a steady job and uses less alcohol.

DR. JACOB FINESINGER: I do not think she is cured yet. We do not know specifically the particular problem she had. Unless you lead onto this problem you do not get far. She identifies with her father. I do not think Dr. Holder suggested that to her. It is rare to have a patient explain her experiences as clearly as this. I should like to spend several hours going over the material. The question of *why* it happened I should leave out; *how* it happened could be interpreted to her. Emphasizing her social adjustment, I would have her become active again and use her leg as much as possible. I would see her once a week. This case illustrates the limitation of this kind of therapy. One can get results like this without going back into childhood material. However, in analysis we would not be satisfied. We would want to know why she had guilt and why she identified. We would attempt to learn about her earlier experiences.

DR. BERNARD BANDLER: Dr. Holder should continue to see her because her father is dying. After his death one can anticipate some reaction. I was interested in the way this came out because the intel-

lectual insight was the last stage. That brought up tremendous effect. The next day she put together the puzzle. The effective thing was her ability to react with emotion while going over this material.

DR. COBB: In order to make a prognosis we must have an accurate and full past history. We must know the number of episodes, the kind of symptoms and how long she has had them. We must evaluate the severity of the emotional crisis which was the immediate precipitant of her present attack. If there is a long past history of numerous episodes with mild precipitants, one is less happy than with a girl like this whose history is not too disturbing.

SUMMARY

A positive diagnosis of hysteria should be made from the clinical picture and from a study of the patient's reactions to life situations. Hysteria occurs mostly in women and typically consists of three components: childishness, conversion symptoms and amnesia. The patient gets into an intolerable situation (conflict) from which she "escapes" by the development of symptoms. She has no memory of the thought processes that have led to such an escape. (The conflict is repressed.) Patients with hysteria often blandly accept their symptoms, and this striking lack of concern has been called "belle indifference."

The symptoms mimic neurologic and medical disorders and include pain, paralysis, sensory disturbances, peculiar gaits, loss of vision, hearing or smell, stiff contracted limbs, vomiting, syncope, fits, hyperventilation and frigidity.

The medical history in this case offered a number of clues. The curious "convulsions" with amnesia strongly suggested hysteria although epilepsy had to be considered and ruled out. Actually there was little resemblance to epileptic seizures, and the electroencephalogram showed no epileptic discharges. The acute attack of abdominal pain with removal of a normal appendix and the episode of unconsciousness and amnesia at college were both

typically hysterical. Finally an unequivocal diagnosis could be made upon the physical findings which were incompatible with a neurologic lesion. As the illness was investigated further and the correlation between symptoms and situations unfolded, the meaning of the conversion symptoms became clear.

In the differential diagnosis of weakness, pain and anesthesia of a single extremity, many possibilities exist. The pathologic process may be inflammatory, toxic, degenerative, traumatic or neoplastic. The lesion may be located (1) in peripheral nerve, (2) in the lumbosacral plexus, (3) in the spinal roots or (4) in the central nervous system. Depending upon the structures affected, various neurologic signs will result.

The important point in this case was that the deep reflexes were normal in the paretic leg. They were brisk and equal to those in the right leg. Babinski's sign was absent. The anesthesia was of the "stocking" type, involving the entire limb from the inguinal ligament down. The muscles of the extremity were weak but there was no atrophy, and the weakness involved the limb as a whole rather than specific muscles or muscle groups. There was neither spasticity nor a true flaccid paralysis. There had never been any disturbance of sphincter control.

A lesion involving peripheral nerve pathways would cause a diminution or loss of deep reflexes, and the sensory loss would correspond to the cutaneous distribution of peripheral nerves or to the appropriate dermatomes. Muscular weakness would involve specific muscles or groups of muscles and the paralysis would be of the flaccid type. In a process of six months' duration one would expect some degree of muscle atrophy.

In a lesion in the tracts of the spinal cord or in the brain deep reflexes would be hyperactive and paralysis would usually be spastic, with Babinski's sign. Ordinarily there would be no sensory loss; but if present, there would be sensory dissocia-

tion, i.e., selective anesthesia according to the tracts involved.

An important differential sign was elicited as follows: With the patient supine, the examiner placed his hands, palms up, under her heels. She was ordered to sit up whereupon both heels pressed down upon the examiner's hands. If the weakness had been due to a neurologic lesion, the *affected leg would not have pressed down* and might even have risen off the table as the patient sat up. (This is known as "Babinski's second sign.")

Characteristically, the paresis in hysteria involves a functional unit as a whole: a hand, an extremity or half the body (with a sharp midline demarcation.) "Glove" or "stocking" anesthesia is typical. The area and degree of anesthesia may vary with repeated examinations or by suggestion on the part of the physician.

In the management of hysteria it is important to avoid frequent examinations and laboratory procedures once the diagnosis has been made. Patients are prone to develop new symptoms and the physician may be tempted to embark upon a further course of diagnostic studies. Examinations and tests should be completed within a few days and psychotherapy instituted as soon as possible.

In the therapeutic interviews a definite plan was followed. First, the emphasis was not upon accumulating a large amount of diffuse material pertaining to all aspects of the patient's life, but rather upon the emotionally significant situations which precipitated the major symptoms. (It would have been interesting to find out more about the episode at college and the appendectomy, but these topics were not in line with the immediate goal and therefore were not discussed in detail.) Second, efforts were made to "focus" the material toward selected limited goals in order to bring out the relationship between situations and symptoms.

The psychiatrist directed the interview with as little activity on his part as possible, encouraging the patient to talk by a show of interest or if necessary by mild commands

such as, "Tell me more about this." Direct questions or leading questions were avoided. No disturbing interpretations were made; although after the patient had seen the relationship between her adopted father's symptoms and her own, the therapist reviewed the material thoroughly with her.

In the staff meeting the limitation of this type of brief psychotherapy was pointed out and prognostic guides were discussed. Further psychotherapy with social service aid was planned. In general the therapeutic process in hysteria is not as dramatic as in this case but is a long term job involving the

combined efforts of the psychiatrist and the social worker. Actually it amounts to an emotional "re-education" process whereby the patient learns new methods of handling life situations, i.e., "grows up."

After discharge from the hospital the patient was seen for a month in the Out-Patient Department and continued to be symptom-free. Her therapist left the hospital staff and she decided that she would prefer not to see another doctor as she felt quite well. She has not returned in nearly two years but reports by telephone that she is still doing well.

Clinico-pathologic Conference

Obesity, Hypertension, Diabetes and Heart Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. G., (B. H. No. 148217), was a fifty-eight year old white married housewife who entered the Barnes Hospital on June 17, 1947, complaining of pain in her chest and back and of obesity.

The patient's father had died of heart disease at the age of fifty-five but otherwise the family history was non-contributory. The patient herself, had had no significant illness in her youth and at the age of twenty she weighed 130 pounds. In the fifteen years following her marriage she gave birth to six normal children, but during this period she gained approximately 200 pounds and reached a maximum weight of 325 pounds which was maintained for about ten years until one year before her death. For ten years prior to admission she had noticed increased hair on her arms, legs and face, and five years before entry she had an episode of vaginal bleeding which lasted several weeks. Dilatation and curettage were performed at an outside hospital and the patient was told that she had no cancer. Subsequent to the operation, however, she received radium treatment. Four years before entry she developed polyuria and polydipsia. She consulted a physician who told her that she had sugar in her urine and she was advised to take 30 units of regular insulin every morning. She followed this regimen for an indefinite period but had taken no insulin for months prior to admission to this hospital. For a period of approximately ten years she had had moderate

dyspnea on exertion and also some palpitation; on several occasions her physician advised her to avoid overexertion because of her heart. Upon a number of examinations she was told that she had high blood pressure but she did not know the levels attained. During the year before entry, although her appetite continued to be voracious, she lost 105 pounds.

Approximately two months prior to entry the patient awakened one morning with a knife-like pain in the left chest which radiated rather diffusely around to the left shoulder and back. The pain was so severe that for two nights she was unable to lie down. She was seen by her physician who prescribed medication which brought some relief, and gradually over the course of a week the pain decreased to the point where the patient was able to resume light household duties. Shortly thereafter, however, pain returned with increased intensity and was noted in both sides of the chest anteriorly and in the back at the level of the scapulae. It was described as being made worse by motion and by deep breathing and eventually became so severe that the patient was almost totally incapacitated. During the month before entry she spent most of each day in a chair. Two weeks before admission she noticed swelling of the ankles which became worse in the evening. Because of these complaints she sought admission to the Barnes Hospital.

At the time of entry physical examination revealed the temperature to be 37.8°C.,

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pulse 84, respirations 18 and blood pressure 220/130. The patient was an extremely obese white female who lay on her left side and screamed with pain when any attempt was made to move her. She was slightly dyspneic but not cyanotic. The fat distribution was chiefly confined to the breasts which were huge and pendulous and to the abdomen where an enormous panniculus extended in front of her. The arms, legs and especially the thighs showed evidence of great weight loss but were comparatively well proportioned. Intertrigo was present in the body folds. The hair on the scalp was sparse and dry but there was a coarse mustache on the upper lip and a moderate amount of black hair on the arms and legs. Examination of the eyes revealed that the pupils were round, regular and equal and reacted well to light and accommodation. The fundi showed normal discs and slightly tortuous vessels. No abnormal findings were noted in the nose, mouth or throat. Examination of the neck was likewise not remarkable; the thyroid was not palpable. Because of the patient's immobility, examination of the lungs and heart was difficult, but there was dullness over the base of the right lung posteriorly and in that area tactile fremitus was decreased and breath sounds diminished. Above this area a few râles were heard. The heart border could not be percussed and the sounds were distant. The rhythm was regular. There was a grade II systolic murmur at the apex and the second aortic sound was accentuated. Because of its huge size, the abdomen could not be palpated properly. Pelvic examination revealed a healed cervical scar and a lax perineum but no other findings could be made out. The clitoris was not enlarged. Rectal examination was negative. There was no lymphadenopathy and the neurologic examination seemed within normal limits. Two plus edema of the ankles was present and there were distended veins over the sixth and seventh dorsal vertebrae.

Laboratory findings on entry were as follows: Blood count: red cells, 4,890,000; hemoglobin, 12.5 Gm.; white cells,

7,950; differential count: eosinophiles, 1 per cent; juvenile forms, 3 per cent; stab forms, 13 per cent; segmented forms, 53 per cent; lymphocytes, 26 per cent; monocytes, 4 per cent. Urinalysis: sugar, trace; albumin, negative; sediment, negative. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: fasting blood sugar, 237 mg. per cent; non-protein nitrogen, 21 mg. per cent; total protein, 6.0 Gm. per cent; albumin, 3.4 Gm. per cent; globulin, 2.6 Gm. per cent; calcium, 11.3 mg. per cent; phosphorus, 5.2 mg. per cent. Venous pressure: 220 mm. of saline. Circulation time (decholin): 15 seconds. Basal metabolic rate: plus 45; plus 49. Roentgenograms: "X-ray of the chest reveals the cardiac shadow to be enlarged 3°. The aorta is tortuous and contains a plaque of calcium in its arch. The trachea appears shifted to the left but the film is not well centered. There is questionable compression of the anterior portion of the body of the 12th dorsal vertebra. There also appears to be a large destructive area in the manubrium sterni. A lateral view of the skull reveals hyperostosis frontalis interna." Electrocardiogram: right axis deviation; occasional ventricular premature contraction.

Shortly after her admission to the hospital the patient was noted to be perspiring profusely and upon close questioning it was learned that similar episodes had occurred frequently for many years. Cyanosis appeared and in view of the other signs of cardiac insufficiency, including dyspnea, cardiac enlargement, increased venous pressure and hydrothorax, the patient was digitalized. She was placed on a controlled diet without insulin although subsequently insulin was given. Further laboratory studies revealed the blood chlorides to be 83 mEq./L., blood sodium 144 mEq./L. and the carbon dioxide combining power 45.2 volumes per cent. A glucose tolerance test was performed and the blood sugar was found to be 321 mg. per cent at four hours and 261 mg. per cent at five hours. A concentration diuresis test showed the specific gravity to range from 1.021 to 1.028. A

phenolsulfonphthalein test was performed and 45 per cent of the dye was excreted in two hours.

A gynecologic consultant was asked to see the patient but because of her weight and inability to cooperate his examination was unsatisfactory.

The patient was seen by an orthopedic consultant who thought that the back pain was due to senile osteoporosis with a compression fracture although it was thought that a metastatic lesion could not be ruled out. A fracture board was placed under the patient's mattress and she was given infra-red treatments with some relief. Aspirin was prescribed in an effort to ease her pain. The patient continued to insist upon lying on her left side. About ten days after admission some of the signs of cardiac insufficiency improved although râles still persisted in her chest. During this period a low grade fever was recorded which was not affected by 30,000 units of penicillin every three hours. About two weeks after admission the patient became rather disoriented, increasingly uncooperative and a very difficult nursing problem. As was stated insulin had been instituted in order to achieve better control of the diabetes and during the third week her fasting blood sugar was 184 mg. per cent. Other laboratory findings included a non-protein nitrogen of 136 mg. per cent, chlorides of 82 mEq./L. and carbon dioxide combining power of 58.2 volumes per cent. Repeated urine examinations showed 3 plus sugar and 3 plus albumin; occasional granular casts appeared in the sediment. Further electrocardiograms showed no change from that on admission except for the appearance of digitalis effect. On the twentieth hospital day the patient became obtunded and during the next several hours her blood pressure rapidly fell to a level of 120/68 and her pulse rose to 110. Her temperature at that time was 38.2°C. Her respirations became rapid and labored. Physical examination failed to reveal evidence of thrombophlebitis in the legs or signs of pneumonia in the chest. However,

the patient became progressively worse and she expired quietly on July 8, 1947.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Before we begin our discussion of this extremely complex case I should like to ask Dr. Bottom if he has any further comments on the x-ray films.

DR. DONALD S. BOTTOM: As was stated in the protocol the films were rather poor, first because of the patient's obesity and second because of her inability to cooperate. The chest film showed marked cardiac enlargement, prominence of the aorta and fluid at the left base. Not only were there marked hypertrophic changes in all of the dorsal vertebrae but also compression of the anterior portion of the body of the twelfth vertebra. No areas of bone destruction were present in the skull.

DR. ALEXANDER: This patient was afflicted in a great many ways: obesity, diabetes, hypertension, arteriosclerosis, cardiac failure, a high metabolic rate and hirsutism all may be listed among her abnormalities. How many of these we may incorporate into our final diagnosis or diagnoses remains to be determined. It seems to me that the most obvious problems were her obesity and diabetes. The endocrinologic aspects of a case such as this are extremely involved and our time is limited. I should like to begin, however, by asking Dr. MacBryde if a single endocrine gland was incriminated primarily in this case.

DR. CYRIL M. MACBRYDE: Taking into consideration the group of symptoms and signs presented by this patient, one would immediately think of the pituitary gland, and I would think it quite likely that there was a disturbance in the anterior pituitary, particularly in the basophil cells. However, I would at once like to qualify my statement by saying that such changes may be associated with other glandular defects and may not be the cause of obesity *per se*. It is known that actual histologic changes in the pituitary are not demonstrable as a rule in any of the usual obesity syndromes and

when one damages the pituitary experimentally no specific type of obesity can be produced. On the other hand, if either the hypothalamus or the supra-optic nuclei are damaged, with or without pituitary injury, obesity often results.

DR. ALEXANDER: You mention the basophilic cells. Do you believe that when the pathologists present sections of the pituitary there will be an organic change in this gland or do you believe that the clinical changes were functional instead?

DR. MACBRYDE: It is most difficult to answer your question. I have seen patients with syndromes clinically similar to those under discussion here in which no pituitary changes were found. On a percentage basis, however, it would seem likely to me that either a basophilic adenoma or hyalinization of the Crooke cells in the anterior pituitary would be present. Indeed, both may be found.

DR. ALEXANDER: Dr. Williams, do you concur in this opinion?

DR. RAY D. WILLIAMS: Yes, I should say there was about a fifty-fifty chance of finding a structural lesion in the pituitary.

DR. ALEXANDER: Do you believe any other structures will be involved in this case?

DR. MACBRYDE: Certainly the adrenal cortex will show abnormalities.

DR. ALEXANDER: Do you think the adrenal changes are due to an adrenotropic hormone?

DR. MACBRYDE: The relationship is obscure. Apparently a connection exists between the pituitary changes and those which occur in the adrenal. In this case there may be diffuse hyperplasia of the cortical cells in either one or both adrenals. It is also likely that one or more adenomas will be present; indeed, in this patient there is the suggestion that there may be a carcinoma. The x-ray findings are consistent with metastatic lesions. You will recall that there was a defect in the sternum and collapse of one of the dorsal vertebrae. Collapse of vertebrae is common in pituitary basophilism on the basis of extreme osteo-

porosis, but I am particularly interested in the sternal lesion and would attribute that more likely to carcinoma; that is, to malignant changes occurring in an adenoma with resultant metastases.

DR. ALEXANDER: You are quite sure then that there will be either hyperplasia and/or adenomas of the adrenal cortex and you further believe that these changes are certainly more apt to be found than pituitary abnormalities.

DR. W. BARRY WOOD, JR.: If there is adrenal cortical adenoma, will there also be Crooke's changes in the pituitary?

DR. MACBRYDE: Yes, the adrenal abnormality is apt to be a tumor in Cushing's syndrome. No basophil adenoma may be found but the Crooke's hyalinization of the basophil cells is practically always present.

DR. ALEXANDER: Dr. Wade, would you comment on the symptoms which may arise as a result of hyperactivity of the adrenal cortex?

DR. LEO J. WADE: Several groups of hormones can be attributed to the adrenal cortex. I think that Fuller Albright's analysis is a good one. As you will recall he attributes some of the symptoms to an "S" or sugar hormone which presumably produces diabetes by interfering with the normal utilization of amino acids; this abnormality is also responsible for osteoporosis because it prevents formation of an adequate bone matrix. It probably has something to do with obesity also for by interfering with amino acid and protein metabolism, fat is produced in abnormal quantities. The masculinizing signs are attributed to an androgenic hormone or hormones—Albright's "N" hormone. Finally there are substances which have to do with salt and water metabolism. Hypertension, which is a common manifestation in this group of patients, is in my opinion difficult to correlate with any of the particular principles.

DR. HENRY A. SCHROEDER: It seems fairly well proven that hypertension depends upon some change in the adrenal cortex because when tumor is present its removal

may lead to disappearance of hypertension. The influence of the salt-retaining hormone on hypertension has been a subject of much speculation recently. There seems to be evidence, in at least some patients with hypertension, that there is some disturbance in salt metabolism. The synthetic salt-retaining hormone, desoxycorticosterone acetate, when given intramuscularly along with salt has been shown to elevate blood pressure in both normal individuals and in hypertensives. Normal patients, however, are much more resistant to this change and it may take a great deal longer to produce any significant change in the blood pressure in normals whereas in hypertensives the change may be seen in a few days or even in one day. In hypertensives intravenous injections of DCA have been found to lead to further elevation of blood pressure.

DR. ALEXANDER: Returning to the obesity, the fat distribution in this woman was apparently not uniform. The lower extremities were described as being fairly well proportioned and most of the adipose tissue was confined to the trunk. Are these facts of significance?

DR. WILLIAMS: The tendency with pituitary basophilism or Cushing's disease is for the fat to become distributed chiefly on the trunk rather than on the extremities. As I recall no mention was made in the protocol as to whether the patient had a "moon" face.

DR. WADE: There is one other possibility that should be mentioned in regard to involvement of the endocrine glands. The change in the sternum might have had something to do with a lesion of the thymus gland. I have never seen such a patient but there are reports in which a tumor or hyperplasia of the thymus gland has supposedly been responsible for changes such as are recorded here instead of a primary lesion of the pituitary or of the adrenal.

DR. ALEXANDER: Do you have any comment, Dr. Bottom?

DR. BOTTOM: There was some discussion in the x-ray department as to whether the sternal lesion could have been an anomaly.

In the lateral view there is certainly no evidence of a mediastinal mass that would suggest a tumor or hyperplasia of the thymus gland.

DR. CARL V. MOORE: I should like to hear further comment on the increased menstrual bleeding. Is it of significance and may it be correlated with the diagnosis of Cushing's syndrome?

DR. MACBRYDE: The patient was fifty-eight years old when she died and the abnormal bleeding occurred five years before entry. We do not know whether she had been amenorrheic prior to this episode of vaginal bleeding or whether she had been menstruating up until that time.

DR. HENRY H. GRAHAM: As far as we could determine there had been no menstrual irregularity previously.

DR. MACBRYDE: Usually when pituitary basophilism or adrenal adenoma is associated with the adrenogenital syndrome and masculinization there is amenorrhea. Patients may have either complete or intermittent amenorrhea but occasionally they do have periods of menorrhagia. In my experience when menorrhagia does occur it usually follows long periods of amenorrhea. Conceivably a similar situation applied here but because of the lack of information I am not able to make any further interpretation.

DR. ALEXANDER: This patient was obese for approximately thirty-five years. In Cushing's syndrome is not obesity usually of more rapid onset? Is it conceivable that this patient had Cushing's syndrome for thirty-five years?

DR. MACBRYDE: In Cushing's disease, with a basophil pituitary adenoma as distinguished from Cushing's syndrome, the course is a rapidly progressive one with sudden appearance of obesity and death of the patient within a few years. The symptoms here are more in keeping with Cushing's syndrome due to adrenal hyperplasia or adenoma.

DR. LLEWELLYN SALE, SR.: What about the possibility of an ovarian lesion?

DR. WADE: I believe that is a good sug-

gestion. The patient might have had either an arrhenoblastoma or a granulosa cell tumor, both of which are known to be masculinizing. When one sees a patient such as this, one of those two tumors should be kept in mind and a careful pelvic examination should be done in an attempt to identify or exclude them. When this patient had the dilatation and curettage, she was told that she had no cancer but she was apparently given radium; and one wonders why that therapy was instituted. She had been hirsute for ten years, however, and I would be skeptical that either an arrhenoblastoma or a granulosa cell tumor would be compatible with survival for that long a period. Either tumor would also leave unexplained the obesity which existed for such a long period of time.

DR. ALEXANDER: Is it conceivable that the patient had an adenoma for some years which subsequently became malignant? In that way perhaps one would explain the long period of hirsutism prior to the terminal illness.

DR. MACBRYDE: I believe that originally benign cortical adrenal adenomas may become carcinomatous.

DR. MARGARET G. SMITH: Some of the large adenomas associated with Cushing's disease have been questionably malignant.

DR. ALEXANDER: This patient had metabolic rates of plus 45 and plus 49, and the curves appeared to be satisfactory. What is your interpretation of these results, Dr. Wade?

DR. WADE: It is difficult to get an accurate measure of the metabolic rate of the patient when one relies upon the determination of the surface area to complete the calculation. The data are certainly unreliable in a patient of this size and therefore I am unable to attach any definite meaning to the basal metabolism recorded.

DR. MACBRYDE: I agree with Dr. Wade's comments, but hypertrophy of the thyroid has been found with changes typical of thyrotoxicosis in Cushing's syndrome.

DR. ALEXANDER: Do you think perhaps

that there may be some hypertrophy of the thyroid gland?

DR. WADE: The patient has a rather low cholesterol which would be in keeping with the diagnosis of thyrotoxicosis but I am not able to substantiate it with any other findings.

DR. ALEXANDER: Now I should like to raise the question as to why this patient suddenly died. At the time of entry she was not cyanotic but subsequently she became so and she had many of the signs of cardiac insufficiency. Dr. Massie, do you believe that she died of a cardiac death because of a failing heart?

DR. EDWARD MASSIE: This is a situation in which the diagnosis of coronary occlusion may certainly find support. The patient was obese, diabetic and hypertensive. She had chest pain in the past and subsequently during her hospital stay her blood pressure fell to a low level and she died. This sequence is quite compatible with a diagnosis of myocardial infarction. Two points, however, stand out against that diagnosis: In the first place the patient had pain which was exquisite when she moved and she had pain when she took a deep breath. Such pain easily could have been due to the lesion in her spine rather than being of cardiac origin. In the second place the electrocardiogram, which of course is not infallible in making a diagnosis of myocardial infarction, does not show any of the changes which are attributable to coronary occlusion. Therefore, on the basis of these two factors I believe that the patient probably did not have a terminal myocardial infarction although I think she in all likelihood did have coronary artery disease.

DR. ALEXANDER: Do you believe that there will be a great deal of fat in the patient's heart?

DR. MASSIE: Yes, I am sure that fat deposition about the heart will be marked and I think there will be ventricular hypertrophy. Further, we should find signs of terminal cardiac failure.

DR. WOOD: I believe that we were suspicious of the possibility of pulmonary

embolism because of the patient's respiratory disturbance and chest pain. As a matter of fact, as I recall it, we considered that diagnosis as an explanation of her original attack.

DR. ALEXANDER: This patient was diabetic and obese. What would you predict as to the findings in her liver, Dr. Moore?

DR. C. V. MOORE: I would expect to find a moderate amount of fatty infiltration but otherwise I should think the liver would appear essentially normal.

DR. MASSIE: In view of the pain in the back and hypertension, dissecting aneurysm should be mentioned in passing as a possible cause of death.

DR. MACBRYDE: For the sake of completeness we should mention that this patient might have parathyroid adenomas which are rather common in this group of patients.

DR. ALEXANDER: We have found today that patients with Cushing's syndrome may have thyroid enlargement, parathyroid adenomas, adrenal cortical abnormalities and pituitary changes. Do they have hypertrophy of the ovaries?

DR. MACBRYDE: At her age it may be difficult to be sure, but when these patients are subjected to surgical explorations, particularly those in the younger age group, atrophy and fibrosis of the ovary are frequently noted. One can say that this disease complex is really a syndrome of multiple endocrine abnormalities with the most striking findings in the adrenal.

DR. WADE: In view of the normal blood calcium and phosphorus do you believe that there is still a possibility of parathyroid adenomas to be considered?

DR. MACBRYDE: Yes I do because usually in these patients the blood calcium and phosphorus are normal.

DR. WILLIAM H. DAUGHADAY: I believe it is necessary to qualify the diagnosis of Cushing's syndrome here for some of the characteristic findings were absent. The patient apparently did not have a plethoric face, and she did not have purple striae which certainly would have been expected in view of the extreme obesity. Further, her

skin was rather thick and somewhat oily in contrast to the usual description in Cushing's syndrome. It would have been helpful to have had determinations of the urinary ketosteroids and the urinary cortins; further, a glucose-insulin tolerance test might have demonstrated insulin resistance but the patient's condition did not permit these studies. The clinical features of this case resemble certain reports, which have appeared mainly in European literature, of "diabetes of the bearded woman" or the Aachard-Thiers syndrome which frequently have been associated with adrenal adenomas. Although adrenal adenomas occur commonly, hyperfunction is relatively rare. The fact that the patient had diabetes, hypertension and hirsutism does not establish the diagnosis of Cushing's syndrome. It has been shown that the incidence of adenoma in this type of case is higher than in the normal; likewise adenomas of the adrenal have also been shown to be associated with hypertension in a greater percentage of cases than in normals and finally, with increasing age itself there are more adenomas.

DR. ALEXANDER: You do not believe there will be a pituitary adenoma or pituitary changes?

DR. DAUGHADAY: I do not believe there will be changes in the pituitary but there may be an adrenal adenoma.

DR. WOOD: We were rather reluctant to make the diagnosis of Cushing's syndrome because we raised some of the same objections which Dr. Daughaday has offered.

DR. ALEXANDER: I believe we are all in agreement that this was indeed a complex problem. The general consensus appears to favor the diagnosis of adenoma of the adrenal cortex possibly with carcinoma and it is thought possible that there will likewise be basophilic changes in the pituitary.

Clinical Diagnosis: Cushing's syndrome; adenoma and/or carcinoma of the adrenal cortex; diabetes; hypertensive cardiovascular disease; cardiac insufficiency; arteriosclerotic coronary artery disease; osteoporosis; ?metastatic carcinoma of the sternum.



FIG. 1. Photograph of the cut surface of one of the adrenal glands showing several tumor nodules.

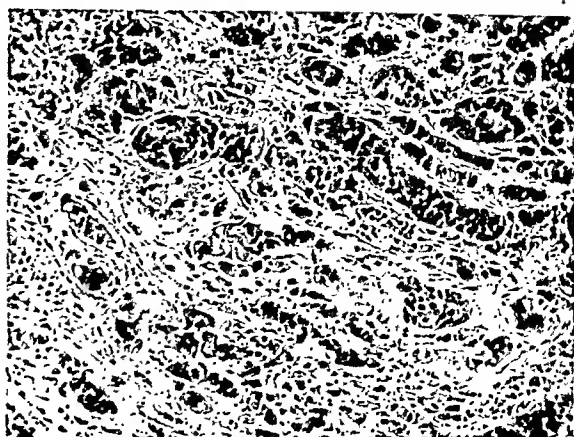


FIG. 2. Section of a lymph node showing an epithelial tumor.

PATHOLOGIC DISCUSSION

DR. JOYCE DAVIS: The body was that of a well developed, obese woman, 155 cm. in length and weighing 95 Kg. The breasts and the abdomen were large and pendulous and excoriation of the skin was evident in its many folds. Over the upper lip and chin there was a moderate growth of stiff black hair. Long black hair was present down the midline of the abdomen and on the legs. There was a broad diastasis of the abdominus recti muscles. As the pleural cavities were being examined the third, fourth and fifth ribs on both sides broke although no undue force was exerted. There were 200 cc. of yellowish, slightly turbid fluid in each of the pleural cavities but none in the peritoneal cavity. A few petechiae were present over the surfaces of the pleural cavities. The heart was hypertrophied and dilated, weighing 420 Gm. A few atheromatous plaques were present in the coronary arteries, but there was very little narrowing of their lumina. There was a patent foramen ovale of the guarded type and a few petechiae were seen over the pericardium.

The liver was large, peculiarly flat and weighed 1,940 Gm. Its outer surface was uniformly nodular as were the cut surfaces. The nodules varied in size from 2 to 3 mm. to 2 to 4 cm. in diameter and a considerable amount of yellowish fat was visible in them; firm, gray fibrous tissue separated them. Lymph nodes in the porta hepatis and in the thorax were enlarged, soft and bulged

from the cut surface. The spleen was large, very soft and mushy and weighed 580 Gm.

The adrenal glands were quite unusual. The right weighed 11.4 Gm., the left 13 Gm. Both measured approximately 9 by 6 cm. Their external surfaces revealed no abnormalities. The cut surfaces, however, presented several fairly discreet, round yellowish-gray areas which differed markedly from the golden yellow color of the normal cortex. (Fig. 1.) After fixation other similar nodules were apparent. In the left adrenal there was also a grayish-white area in the medulla that was not as vascular and was much thicker than the medulla in the rest of the gland.¹

DR. MARGARET G. SMITH: We shall have to rely upon the microscopic findings in order to arrive at a final diagnosis in this case. The large greyish-white lymph nodes were interpreted as containing tumor and we thus were faced with the problem of deciding where the primary tumor arose. No tumor was seen in the gross in any of the solid organs other than possibly in the adrenal glands where the nodules which Dr. Davis described were found. Beside a malignant tumor obesity, hirsutism, osteoporosis, cardiac enlargement and a clinical history of hypertension and diabetes were

¹ At the time of autopsy the sternum appeared grossly normal and only a routine section was made; through an oversight the pathologist was not apprised of the x-ray changes in the sternum and thus did not make a more detailed study.

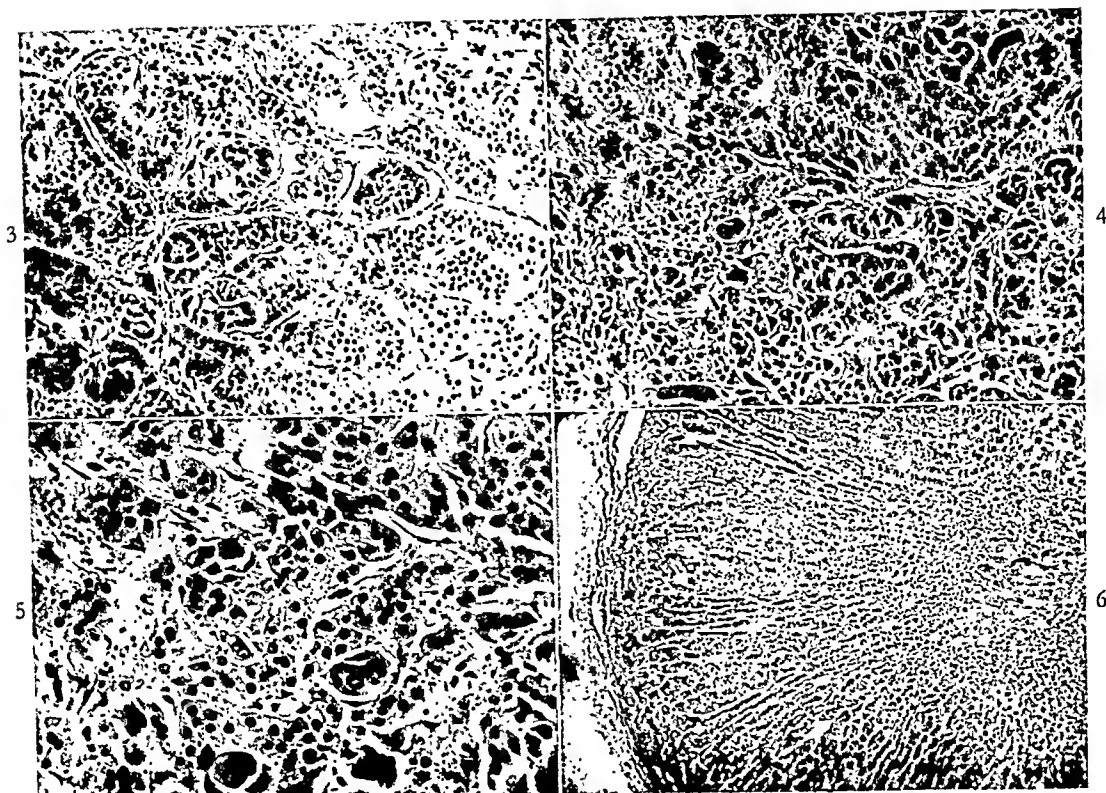


FIG. 3. A section of the adrenal gland through an area of focal hyperplasia.

FIG. 4. Another section of the adrenal through a nodule which shows definite malignant cells.

FIG. 5. High power view of the section seen in Figure 4. The character of malignant cells can be well seen here.

FIG. 6. An area of the adrenal cortex which does not show any focal hyperplasia. Note that the reticular zone appears quite wide.

present, all of which would be compatible with some major endocrine disturbance.

A section of one of the lymph nodes (Fig. 2) showed an epithelial tumor with considerable fibrous tissue proliferation. The tumor cells did not have a glandular arrangement; most of them had considerable cytoplasm, the nuclei varying from a vesicular type to a type with a smaller, deeply chromatic nucleus. From the appearance of the tumor in the node it was not possible to state where it arose, but it was certainly an undifferentiated epithelial tumor growing in sheets and cords. In another section of a lymph node there was necrosis in the center of some of the tumor nodules with calcification within the necrotic areas. The next section (Fig. 3) is from the adrenal and shows one of the multiple areas of focal hyperplasia. Similar changes were found in many other sections from the adrenal glands but these areas

varied considerably in appearance. In some parts isolated cells closely resembled those from the cortex of the adrenal glands whereas in others the cells did not contain vacuoles and were deeply eosinophilic. In still other areas there apparently was further change in the cells so that they resembled the normal cortical cells even less. They had larger nuclei and more cytoplasm and were arranged in sheets. A section from another nodule (Fig. 4) shows definitely malignant cells. These cells are large and have deeply eosinophilic cytoplasm; their nuclei show considerable variation in size and chromatin content. The normal arrangement of cortical cells is lost. A higher power view of the preceding section (Fig. 5) shows the malignant character of the cells.

When one studied these sections of the adrenal, the tumor did not seem to have arisen in a single large nodule but rather from multiple adenomas or focal areas of

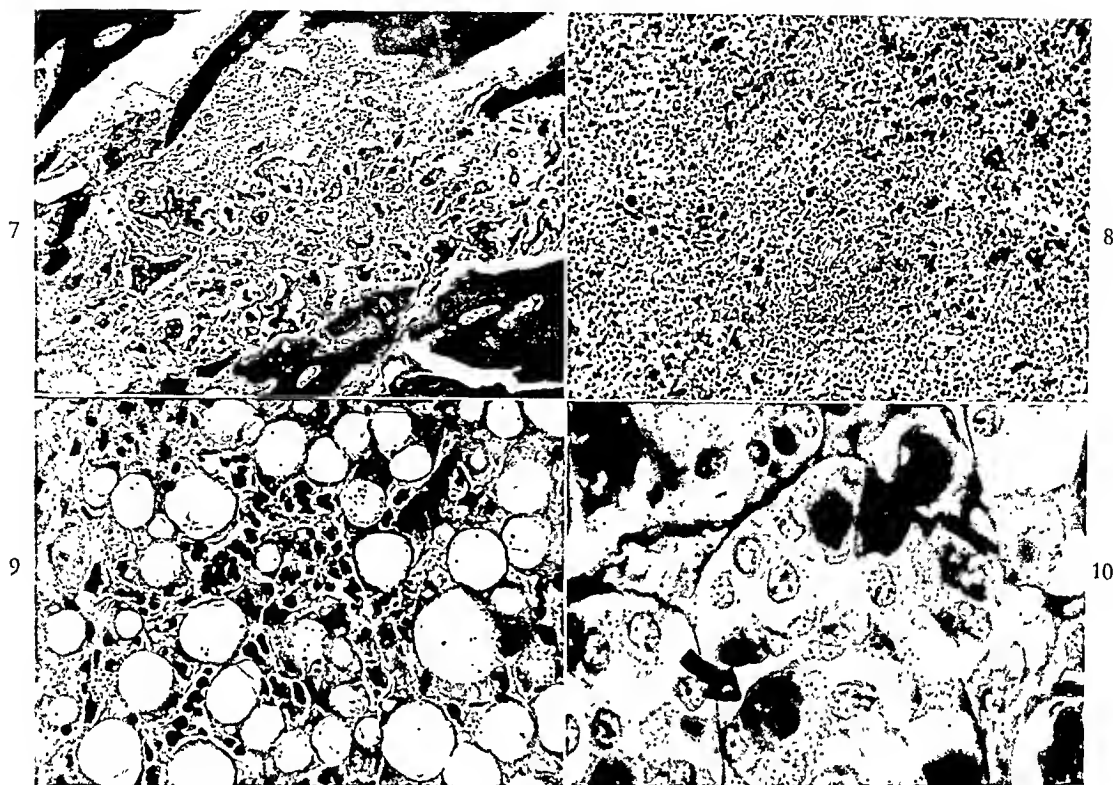


FIG. 7. Section from a vertebra showing infiltration of the tumor cells in a dense connective tissue.

FIG. 8. An area in the spleen where extramedullary hematopoiesis is quite prominent.

FIG. 9. Section of the liver showing fatty metamorphosis and hematopoiesis.

FIG. 10. Section of the pituitary in which the basophilic cells show Crooke's changes. Note particularly the cell indicated by the arrow.

hyperplasia. Because of our difficulty in deciding where the tumor arose, we were at first loath to consider it primary in the adrenal. It might have been metastatic to the adrenal, but there was no evidence of a malignant tumor elsewhere. Further, as we considered the relationship of the tumor to areas of focal hyperplasia the apparent transition in some areas was so striking that we concluded that this was indeed a carcinoma of the adrenal involving both glands. Probably the tumor rose in areas of hyperplasia in the cortex which in all likelihood were present for a long time.

Figure 6 is from an area of the cortex not showing the changes of focal hyperplasia. It is interesting that the reticular zone appears wide in this gland in comparison with the fascicular and glomerular zones. In some places one can see the pigmented cells of the reticular zones extending in strands up into the fascicular zone. The

fascicular zone also seems to be hyperplastic throughout.

The next section (Fig. 7) is from a vertebra. There is a large amount of connective tissue and a small amount of new bone formation. Strands and sheets of tumor cells may be seen in the dense connective tissue. No hematopoiesis is seen in this section.

In the spleen (Fig. 8) there were numerous islands of extra medullary hematopoiesis of both erythrocytic and granulocytic cells. In the liver (Fig. 9) there was also a considerable amount of hematopoiesis and marked fatty metamorphosis.

The pituitary gland showed many eosinophiles but there was no adenoma. Some of the basophiles were normal in appearance; in Figure 10, however, there is seen a basophile (arrow) which shows degranularization and homogeneous cytoplasm containing vacuoles. With a differential stain

for cell granules, it was found that the non-granular cytoplasm of these cells was of the robin's egg blue color described by Crooke. This is the type of degranularization and hyalinization of the cytoplasm that one finds in Cushing's syndrome.

A section of the kidney showed some thickening of the basement membranes in the glomeruli but there was a surprisingly small amount of arteriolar change in view of the marked hypertension. In the pancreas there were many normal islands but some showed hyalinization.

In summary, we believe that the areas of focal hyperplasia in the adrenals probably had been present for some years and were related to the endocrine disturbance. More recently there were malignant changes in the areas of hyperplasia and subsequently metastases to the lymph nodes and bone marrow. As a result of destruction of the marrow, extramedullary hematopoiesis occurred. As far as the terminal episode is concerned the patient had fluid in her chest, an enlarged heart and other findings consistent with cardiac failure although there was not the marked degree of congestion in the liver and lungs that one usually finds under such circumstances.

DR. C. V. MOORE: It seems almost impossible that the blood count recorded on this chart is correct, and it is difficult to refrain from making some comment about it. The differential must have been incorrect. With so much extramedullary hema-

poiesis and so much infiltration of the bone marrow, the patient must have had myelocytes or nucleated red blood cells or both in her peripheral blood. If those had been recognized, it would have pointed definitely to a myelophthisic process and the tumor might well have been diagnosed before death.

DR. ALEXANDER: Is this not a most unusual form of carcinoma?

DR. SMITH: Yes, it is. It is so unusual that to begin with I maintained that it was a metastatic tumor in the adrenal but I am now convinced that it was primary in the adrenal.

Final Anatomic Diagnoses: Focal hyperplasia of adrenal cortex; obesity (96 Kg.); hirsutism; osteoporosis; hyalinization of cytoplasm of basophil cells of pituitary gland; hyalinization of islands of Langerhans (history of diabetes); arteriolar nephrosclerosis, slight (history of hypertension); hypertrophy and dilatation of the heart (420 Gm.); carcinoma of adrenal cortex; metastatic carcinoma in porta hepatic, peripancreatic and tracheobronchial lymph nodes and in lymph nodes of the transverse mesocolon; metastatic carcinoma in the bone marrow, advanced, and in the liver; extramedullary hematopoiesis in the spleen and liver.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Lupus Erythematosus Disseminatus Sine Lupo with the Nephrotic Syndrome*

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THE criteria for the clinical diagnosis of lupus erythematosus disseminatus have been well formulated. The cardinal features are: (1) The erythematous lesion of the skin, frequently in butterfly distribution over the face; (2) constitutional symptoms of pyrexia, weakness, cachexia and loss of weight; (3) negative blood cultures; (4) arthralgia; (5) nephritides; (6) suppression of blood-forming elements, including leukopenia, secondary anemia and thrombocytopenia; (7) lymphadenopathy; (8) endocarditis (non-bacterial); (9) effusions into pericardial, pleural and less commonly, the peritoneal cavities; (10) predominant occurrence in females.

The above protean manifestations occur singly or in various combinations and are of varying duration. Until recently the skin lesion was thought essential for diagnosis but the analysis of Gross and Friedberg¹ in 1936 established the concept of disseminatus lupus erythematosus sine lupo.

This case is described because there are so few specific reports of the disease without the skin component.

CASE REPORT

E. C., a thirty-four year old unmarried white female of Italian parentage, was admitted to the Fourth Medical Division of Bellevue Hospital on April 18, 1946, complaining of intermittent swelling of the hands, legs and feet for the past two years.

Two years ago the patient developed intermittent attacks of painful and swollen fingers which were aggravated by cold weather. Asthenia, nocturia and polyuria became evident in the past year. In January, 1946 edema

of the ankles developed, soon followed by swelling of the face, legs and hands which became progressively more severe and which persisted. Mild exertional dyspnea, without orthopnea, occurred at this time. Urinalysis revealed massive albuminuria. She was treated with a high protein diet but showed no improvement. In April, 1946 the patient developed frequent nausea and vomiting, accompanied by marked lethargy. One month before admission a detailed examination by her private physician revealed the following: Generalized edema; blood pressure, 144/88; marked albuminuria with a specific gravity of 1.008 to 1.014; severe secondary anemia; leukopenia; cholesterol, 267 mg. per cent; non-protein nitrogen, 74.2 mg. per cent; serum phosphorus, 6.4 mg. per cent and total protein, 4.1 Gm. per cent (albumin 2.9 Gm., globulin 1.2 Gm.). A diagnosis of chronic diffuse glomerulonephritis with marked impairment of renal function was made at this time.

Review of systems was non-contributory. The patient smoked two packages of cigarettes daily. She had typhoid fever as a child, frequent sore throats and colds until six years before admission and chronic bilateral otitis media since childhood with intermittent purulent discharge. There was no history of rheumatic fever, growing pains, joint pains or epistaxis. Her mother died at the age of thirty-nine from pneumonia and her father died at the age of seventy-two from arteriosclerosis. Three brothers and four sisters were all alive and well. There was no known history of kidney disease, tuberculosis, cancer, rheumatic fever or allergic disease.

Physical examination revealed the following: Temperature, 98.6°F.; pulse, 80; respirations, 20; blood pressure, 180/100. The patient was in no distress; she appeared to be her stated age

* From the service of the Fourth Medical Division, Bellevue Hospital, New York, N. Y.

and was well developed and fairly well nourished. There was 2 plus peri-orbital edema. The mucous membranes were pale and there were no hemorrhages. The head revealed no scars, deformities or mastoid tenderness. There was no gross disturbance of vision. The pupils were round, equal, regular and reacted to light and accommodation. Nystagmus was absent; external ocular movements were normal. Examination of the fundi was within normal limits. The right drum of the ear was perforated, with obliteration of landmarks but no discharge. The left drum was scarred, thickened and retracted. No perforation was seen. There was impaired bilateral hearing. A small amount of encrusted mucus was present in the nose but there was no obstruction. The septum was intact. The tongue was pale but otherwise normal. Teeth were in poor repair and were carious. Tonsils were normal in size and there was no exudate or injection. There was no venous engorgement or abnormal pulsation in the neck. The anterior cervical glands were palpable bilaterally. The trachea was in the midline. The thyroid was not enlarged. The chest was symmetrical and expansion was equal. Breasts were of normal size and there were no scars or tenderness. No masses were palpable. The lungs were resonant and the breath sounds were vesicular. Tactile and vocal fremitus were normal; no râles were heard. The apex beat of the heart was in the fifth interspace at the mid-clavicular line. Cardiac dullness was within normal limits. No thrills were palpable. Sounds were of good quality; a blowing systolic murmur was heard at the apex transmitted to the pulmonic area. The pulmonic second sound was accentuated compared to the aortic second sound. There was regular sinus rhythm. The abdomen was slightly distended; it was soft and there was no tenderness. The liver, spleen and kidneys were not palpable. The genitalia were normal; rectal examination was normal. Vaginal examination showed that the uterus and adnexa were normal. There was a small cervical erosion with slight leukorrhea. There were moderate sized lymphatic glands palpable in the anterior cervical, axillary and inguinal regions. There was no clubbing of the fingers or cyanosis. Four plus pitting edema of both ankles was present. The cranial nerves were intact and there was no tremor present. Motor power was good. All deep tendon reflexes were 3 plus and equal. Superficial reflexes were normal. No abnormal

pathologic reflexes were seen. Sensations were normal.

Laboratory studies revealed the following: Urinalysis on admission, pH 4.5; specific gravity, 1.015; albumin, 4 plus; glucose and acetone negative; microscopic examination showed frequent white blood cells, moderate red blood cells and frequent granular casts. Throughout the hospital stay the specific gravity ranged between 1.011 and 1.022; albumin was 4 plus, with moderate white blood cells, red blood cells and granular and hyaline casts. Urine revealed *Streptococcus viridans* on April 29, 1946; gamma streptococcus on May 7, 1946. Blood counts on admission: red blood cells, 2,430,000; hemoglobin, 7 Gm.; white blood cells, 5,000; polymorphonuclears, 73; transitionals, 3; lymphocytes, 19; monocytes, 2; eosinophiles, 3; slight hypochromia and poikilocytosis were noted on the blood smear and the platelets appeared to be increased. Throughout the hospital stay the red blood cells ranged between 2,350,000 and 3,450,000; hemoglobin between 7 Gm. and 8.5 Gm.; white blood cells between 4,200 and 5,000 until 21,800 on the day of death. There was little change in the differential blood counts except for an eosinophilia of 8 per cent on one occasion. Ninety-six per cent polymorphonuclear cells were seen on the day of death.

The blood cultures were sterile; the sedimentation rate was 69 mm. in one hour. Blood chemical studies showed that the non-protein nitrogen was 75 mg. per cent on admission and it rose to 112 mg. per cent; total protein, 4.8 Gm.; albumin ranged from 2.2 to 2.6 Gm.; globulin from 2.5 to 2.2 Gm.; cholesterol was 420 mg. per cent on admission and fell to 250 mg. per cent; cholesterol esters 143 mg. per cent; urea nitrogen from 45 to 56 mg. per cent; creatinine from 2 to 5 mg. per cent; sugar 118 mg. per cent; CO₂ combining power from 40 to 50 vols. per cent; serum calcium 12 mg. per cent. Blood Wassermann was negative. Phenol-sulphonphthalein test showed 5 per cent excretion in fifteen minutes, 10 per cent in thirty minutes, 20 per cent in one hour, 35 per cent in two hours. Venous pressure in the right arm was 125 mm. of water and in the left arm 150 mm. of water. Circulation time with decholin was 14 sec. and with ether 7 sec. X-ray of the chest April 24, 1946, revealed that the heart was not enlarged in the transverse diameter. No enlargement of the left auricle was visible

upon barium swallow. There was small effusion in the horizontal fissure of the right lung. In May 13, 1946, there was pneumonic consolidation in the lower two-thirds of the right lung and in the middle third of the left lung. Electrocardiograms showed regular sinus rhythm, low voltage, left axis deviation and P-R interval of 0.16 seconds. Subsequent electrocardiograms showed a sinus tachycardia with no other diagnostic alterations.

For the first four days of the patient's course in the hospital her temperature was normal, but for the remainder of the patient's stay she ran a low grade remittent fever up to 101.8°F. Dyspnea at rest which was not present on admission became a prominent symptom after the second hospital day. The patient was treated for an acute exacerbation of chronic glomerulonephritis. In view of the chronic otitis media as a possible focus of infection a course of penicillin was given for eight days (20,000 units every three hours intramuscularly). The febrile toxic course continued and penicillin was discontinued. On the ninth hospital day swelling of the left hand, with pain in the left elbow and right hand, was noted. Fluid was found at both bases with occasional râles at the left base. A flame-shaped hemorrhage was seen in the retina, with narrowing of the retinal vessels. The previously heard systolic murmur was intensified and a diagnosis of acute rheumatic fever was entertained. Several observers noted an apical presystolic murmur. The patient received 80 gr. of salicylates a day. This medication was maintained for one week, to the point of mild toxicity, with no relief of pyrexia or joint manifestations. Two blood transfusions were given, with only temporary elevation of red count and hemoglobin. On two occasions the patient developed a chill and went into acute pulmonary edema while receiving intravenous infusions of Hartmann-Ringer's solution and blood plasma. The patient responded favorably to the usual emergency measures.

On the twenty-third hospital day the patient complained of precordial pain and a pericardial friction rub was heard at the apex. The diagnosis of acute rheumatic fever was reconsidered and salicylates were started again with no apparent effect. On the twenty-fourth day all the clinical and laboratory findings were reviewed. In order to fit the entire clinical picture into one pathologic entity the tentative clinical diagnosis of disseminated lupus ery-

thematosus sine lupo was suggested, and the diagnosis of acute rheumatic fever was discarded.

The patient became severely dyspneic, orthopneic and cyanotic on the evening of the twenty-fourth day. Pulmonary edema developed but she responded fairly well to oxygen and intravenous aminophylline. On the twenty-sixth hospital day she again developed severe pulmonary edema, and the possibility of pericardial effusion with tamponade was considered. However, since the venous pressure was 130 mm. of water and the heart sounds were heard clearly, a pericardial tap was not considered advisable at that time. The blood pressure had ranged between 180/100 and 214/128, but on this day it was 144/92. She was given morphine, intravenous 50 per cent glucose and aminophylline, with little effect. On the twenty-seventh day pulmonary edema continued in spite of oxygen and the usual therapy. The heart sounds were well heard and not muffled. The pulse was rapid and regular. No pericardial rub could be heard. The cardiac dullness was enlarged to the left anteriorly and below the angle of the left scapula posteriorly. The liver was palpable and there was generalized edema. A phlebotomy of 325 cc. was performed, with some relief of the dyspnea. X-ray of the chest did not reveal any pericardial effusion. The patient was digitalized parenterally, with no apparent improvement. A positive pressure respirator was applied. A pericardial tap was attempted anteriorly and posteriorly, but no fluid was obtained. The patient continued in pulmonary edema despite energetic therapy and became unconscious while in the positive pressure respirator. She expired on May 14, 1946, the twenty-seventh hospital day.

* At autopsy the gross findings were as follows: The body was that of a thirty-four year old white woman, 162 cm. in length, and weighing approximately 135 pounds. The skin was quite pale. No petechiae were seen. Pitting edema of both ankles was present.

The peritoneal cavity contained about 100 cc. of clear, pale yellow fluid. The peritoneal surface was smooth and glistening. The edge of the liver extended 2 cm. below the right costal margin in the mid-clavicular line. The right pleural cavity contained 75 to 100 cc. of clear, light

* We are grateful to Dr. Stanley Gross of the Department of Pathology, Bellevue Hospital, New York, N. Y., for the complete autopsy protocol.



FIG. 1. Photograph of the heart showing verrucae on the mitral valve.

yellow fluid. The lung lay free in the pleural cavity. The left pleural cavity contained 75 to 100 cc. of bloody fluid. The left lung lay free except for one firm adhesion between the parietal wall and the posterior portion of the left upper lobe. On the outer surface of the parietal pericardium there was a pinpoint hemorrhage and blood clot, without evidence of perforation of the pericardium or myocardium. There were a few pleuropericardial adhesions on the left. The pericardial cavity contained 75 cc. of cloudy, grey fluid. Thin, long strands of fibrin were seen floating in the fluid and a few strands extended from the visceral to the parietal pericardium.

The heart weighed 420 Gm., but did not appear dilated. The pulmonary artery contained only postmortem clots. Both auricles were of normal size and the auricular appendages were clear except for postmortem clots. The tricuspid valve leaflets were thin and delicate and the chordae tendineae were long and thin. The mitral valve leaflets were thin and fairly delicate. On the auricular surface of the aortic leaflet of the mitral valve near the free margin there were two small pinhead-sized verrucae which appeared greyish white to yellowish white in color and were firmly attached. (Fig. 1.) A few chordae tendineae appeared to be slightly thickened but there was no fusion or shortening. The aortic valve leaflets were fine and delicate. The myocardium was firm and pinkish in color. No areas of fibrosis were seen. The coronary arteries were patent throughout, were not tortuous and the walls were not sclerotic. There was some mottling of the intima by pinpoint yellow atheromatous deposits, particularly in the right coronary artery and the initial portion of the left coronary artery. The right

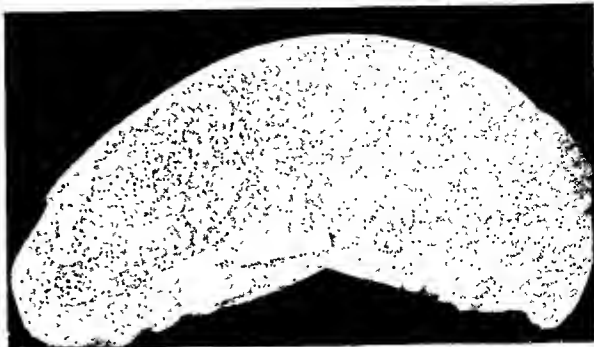


FIG. 2. Photograph of spleen showing malpighian bodies as prominent small grey nodules.

ventricular wall was somewhat hypertrophied and thickened. Culture of the heart's blood taken at autopsy was sterile. There were many pinpoint intimal deposits of yellow material in the arch and ascending portions of the aorta.

The left lung weighed 790 Gm., the right lung weighed 940 Gm. The right lung was subcrepitant throughout and was firm. The pleura over this lung was smooth. The cut surface of both upper and lower lobes appeared somewhat brownish. The parenchyma was somewhat airless and frothy fluid was expressed from the cut surface. The bronchi contained frothy fluid but the mucosa appeared normal. The left lung was fairly firm throughout and quite firm in the region of the fibrous adhesions. In this area the lung surface was puckered and a deep scar was evident. Over the lateral surface of the lower lobe was seen a small area covered by a loosely adherent blood clot. The cut surface of the left lung showed a few scattered areas of consolidation which felt firmer than the surrounding tissue but did not stand out from it. The bronchi were as described in the right lung. Hilar and tracheal-bronchial nodes appeared slightly enlarged and succulent and on section showed a grey-black color.

The liver weighed 1,630 Gm. Mild congestive changes were present; otherwise, the liver was not remarkable.

The spleen weighed 230 Gm.; the surface was smooth, the capsule was thin and the organ appeared pinkish-grey. The cut surface was flat and malpighian bodies stood out prominently as small grey nodules each about 4 mm. in diameter. (Fig. 2.) The trabeculae were not prominent. The splenic pulp was somewhat firmer than usual. There was a small accessory spleen about 1 cm. in diameter in the gastrosplenic ligament.



FIG. 3. Spleen showing periarterial fibrosis ("onion skin"); hematoxylin and eosin stain, $\times 220$.

The right kidney weighed 280 Gm. and the left kidney weighed 250 Gm. Both kidneys were very large, pale and soft and closely resembled a "large white kidney." The capsules stripped with ease and smooth, grey-white waxy surfaces were seen. There were a few thin red streaks mottling the surface. On section the surface of the kidney did not bulge and appeared pale, waxy and yellow. The cortex on the right was 7 mm. wide and on the left 5 mm. wide. Cortical-medullary differentiation was fairly distinct. The pelves and ureters appeared normal.

Axillary, inguinal, retroperitoneal, posterior mediastinal, cervical and mesenteric lymph nodes were all enlarged. The nodes were soft, succulent, discrete and on section the surface bulged slightly and appeared pink-grey.

The vertebral bone marrow was pale pink throughout; the bony architecture appeared normal.

The neck organs were essentially normal except for mild edema of the arytenoid region. The thyroid was normal in consistency and on section showed a gelatinous shiny surface. Two parathyroids were identified and appeared grossly normal.

The pancreas, adrenals, gallbladder, biliary ducts and urinary bladder were all grossly normal.

The genital tract was not remarkable except for several small, simple cysts of the ovaries.

Mild congestive changes were present in the gastrointestinal tract; otherwise, it was normal.

The dura of the brain was smooth and glistening. The leptomeninges were thin and delicate. The brain weighed 1,180 Gm. The middle ear on the right was opened and a small amount of serous fluid was seen. On the left the middle ear revealed a moderate amount of glairy fluid. The brain appeared normal to the naked eye and no microscopic sections were taken.

Microscopic findings revealed the following: The auricular and ventricular endocardium of the heart showed no significant changes. The myocardial fibers had distinct cross striations and occasional fibers had small vacuoles. There was a slight increase in connective tissue around occasional blood vessels but no marked cellular response was found. No Aschoff bodies were seen. The mitral valve leaflet, in the distal third, revealed a flat thickening of the endocardium and subendocardial connective tissue on the auricular surface. This thickening was composed of hyaline material. Occasional clumps of pink-staining collagenous material appeared deeply eosinophilic but not smudgy. The pericardium showed changes consistent with the pericarditis described in the gross findings. The serous lining was thickened and a few cells were deep in places. The tricuspid valve leaflet showed no significant changes.

Both lungs showed similar pictures. Many alveoli contained and some were filled with an exudate made up of red cells, fibrin, polymorphonuclear cells, large mononuclear cells, some with reniform nuclei, and other large mononuclears with brown granular pigment. Some alveoli contained moderate to marked numbers of pigment-bearing macrophages. Some alveoli contained edema fluid and in some cases were partially lined by hyaline eosinophilic material. Some of the septal walls were infiltrated by polymorphonuclears and mononuclears. There was moderate congestion throughout the bronchial and bronchiolar walls. The small vessels, particularly capillaries and venules, showed a lifting of the endothelium and there was some pink fibrinoid material deposited beneath. The larger vessels did not show marked changes. The left pleura of the

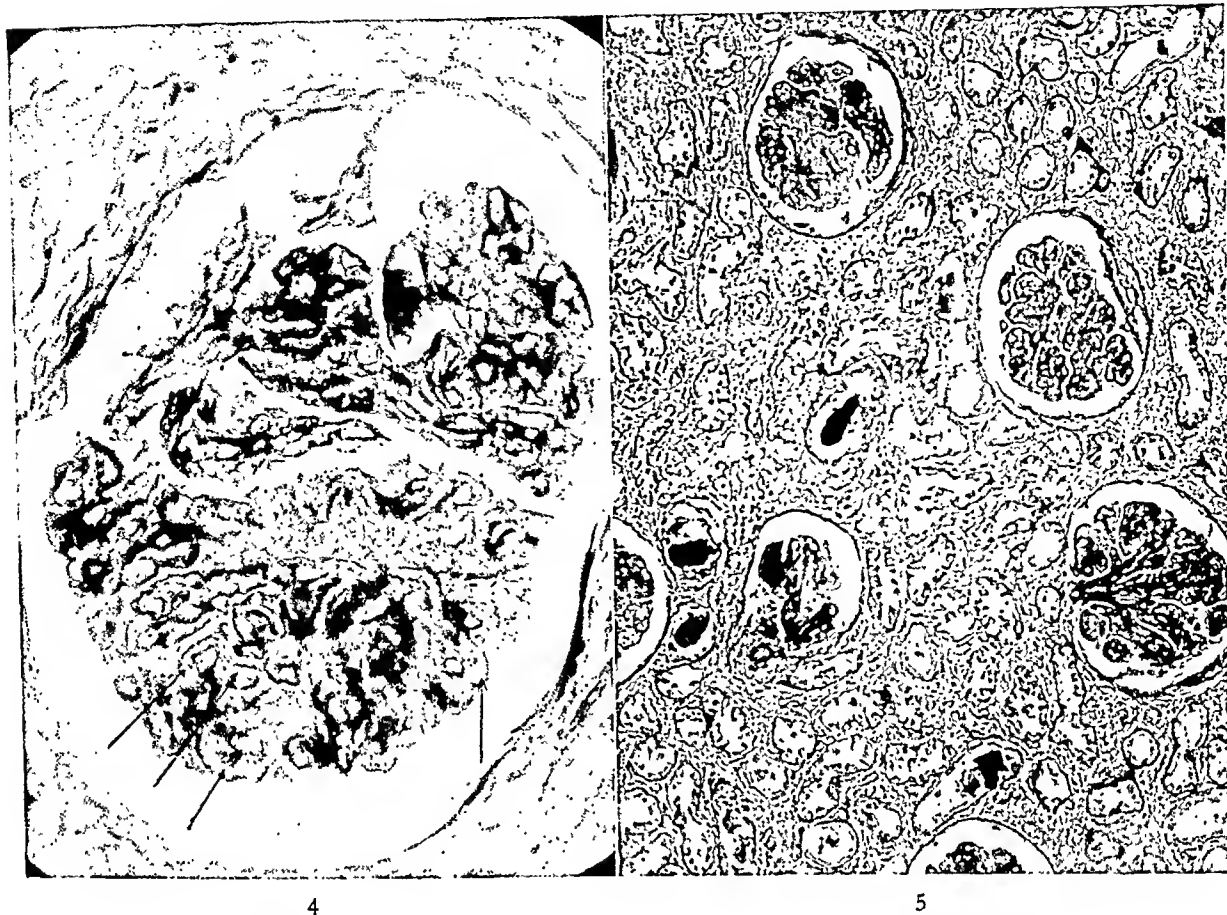


FIG. 4. Thickening of the basement membrane of glomerular loop by hyaline material with "wire-loop" formation; azancarmine stain, $\times 550$.

FIG. 5. Photomicrograph of kidney showing wire-loop formation, glomerular crescents, intercapillary sclerosis and atrophic tubules occasionally filled with hyaline casts; azancarmine stain, $\times 220$.

lung was slightly thickened and there was fibrin deposited on the surface.

In the spleen the malpighian bodies were cellular and stood out because of the peculiar configuration of the central arterioles. These vessels, the smaller arterioles in the red pulp and some of the arteries in the trabeculae were ringed by pink concentric lamellae which stained blue with azancarmine and produced an "onion-skin" appearance. (Fig. 3.) In addition, there was deposition of pink-staining material subintimally in some of these vessels, particularly the smaller arterioles. The sinusoids were moderately distended and congested. The endothelium was fairly prominent. An occasional megakaryocyte was seen and there were small collections of large mononuclears. Occasional polymorphonuclears and eosinophiles were seen in the sinusoids as well as some brown pigment-bearing macrophages. Large and small veins showed diffuse and focal infiltration of the intima with small and large mononuclears.

Sections of the kidney showed marked alteration of all structural elements. The glomeruli were often swollen and appeared larger than normal. Many were markedly anemic and a rare one was congested. The glomerular loops were often simplified and some had adhesions binding them to a thickened Bowman's capsule. Of note was the thickening of the basement membrane of some glomerular loops by deep pink-staining hyaline material. The appearance of these loops was suggestive of the so-called "wire loop" lesion, (Fig. 4) and with azancarmine this hyaline material stained red or occasionally reddish blue. These glomeruli also showed nuclear fragmentation. Occasionally, there was some evidence of intercapillary sclerosis. Bowman's capsule was often thickened by crescent formation. (Fig. 5.) Many of these were epithelial but often they were made up of fibrous tissue. These crescents and the thickened capsule stained blue with azancarmine. Many of the tubules were atrophic and lined by

flattened epithelium. Some tubules were filled with hyaline casts. Groups of tubules were dilated and filled with smudgy, deeply eosinophilic casts. There was a diffuse increase in loose connective tissue and focal areas of fibrosis were seen. A moderate number of small arterioles and medium sized arteries showed some intimal thickening which stained blue with azan-carmin. Fat stain showed scattered granules of red-staining material in glomerular cells, in tubular epithelium and occasionally in hyaline casts.

The lymph nodes showed reticulo-endothelial hyperplasia.

The bone marrow was quite cellular and appeared moderately to markedly hyperplastic.

The pancreas was normal microscopically and the vessels showed no remarkable changes.

PATHOLOGY

Lupus erythematosus disseminatus affects the kidneys in such a high percentage of cases that this feature may be regarded as an integral part of the disease.²

The diversity of pathologic renal findings is very striking. Mallory^{3,4} described kidney changes as very minimal; an occasional glomerulus showed glomerulitis of a tuft or a portion of a tuft and the convoluted tubules were a little swollen. Nephritis was diagnosed in 70 per cent of his cases. Stiekney and Keith⁵ described fifteen cases, eight of which showed no definite change other than that seen terminally in debilitating diseases. They found a proliferation of the endothelial cells of the glomerular capillaries with hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane. They regarded these changes as somewhat similar to those found in acute glomerular nephritis⁶⁻⁸ and the toxemias of pregnancy. The lesions were considered secondary to the toxic processes and did not represent primary renal disease. Keith⁹ summarized the renal findings as follows: "Renal insufficiency does not play an important role causing death, since chronic uremia very seldom occurs. The histologic changes in the kidneys are almost never as extensive as those seen in progressive glomerulo-

nephritis of similar duration. The usual renal lesions, particularly those of the glomerulus, may resemble lesions found during the first two weeks of acute glomerulonephritis. But in lupus erythematosus renal anomalies such as albuminuria, cylindruria, and microscopic hematuria may persist for two or three years in contrast to a few weeks in the former condition and yet similar histologic findings be present. This fact suggests that the renal threshold in lupus erythematosus is a mild reaction to a toxic agent with minimal scar formation. Further study has indicated that this renal lesion is non-specific and can be produced in various toxic conditions as for example, lupus erythematosus, ulcerative colitis, and peritonitis. In some of these cases were found albuminuria varying periodically from grades 1 to 4 and at necropsy only minor histologic changes in the glomerulus. Such findings suggest that the renal lesion may be temporarily reversible and analogous to what sometimes occurs in the skin lesions."

Baehr, Klemperer and Schiffrin¹⁰ first described the "wire-looping" in the glomerular tuft due to a peculiar thickening of the walls of the glomerular capillaries which did not contain amyloid or lipoid material. Along with these changes they described proliferative and thrombotic processes involving part or all of the glomerular vasculature; the picture might resemble that of the embolic glomerulonephritis seen in subacute bacterial endocarditis.^{11,12} Klemperer, using the Mallory connective tissue stain, believes that the wire loops indicate a fibrinoid degeneration and collagenization of the basement membrane. This wire-loop appearance was not constant, but they claimed to be able to distinguish the wire-loops in lupus erythematosus from those occurring in eclampsia, renal amyloidosis and malignant nephrosclerosis. However, they stated that the morphologic aspects of fully developed vascular necrosis obtaining in accelerated arteriosclerosis and in lupus erythematosus are indistinguishable. Mallory³ was able to find the wire looping in

only one-half of the patients at the Massachusetts General Hospital. Baehr, Klemperer and Schiffrin¹⁰ in their original description said: "The wire-looping lesion was not seen in any other human disease, except perhaps eclampsia." They also mentioned the glomerular and vascular lesions described by Wadsworth in horses which had been immunized by repeated intravenous injections of live bacteria especially of the pneumococcus and streptococcus group. Baehr et al.¹⁰ found hypertension relatively uncommon, whereas Rose and Pillsbury¹³ found hypertension in approximately one-half of their patients. Of those that came to necropsy (five cases) none had hypertension but they did show the wire-loop appearance of the glomerular capillaries, focal necrosis and varying degrees of cellular proliferation, avascularity and ischemia. No gross characteristics were seen in the kidneys. The pathologic diagnosis was focal glomerulonephritis in three patients and atypical diffuse glomerulonephritis in two. Cloudy swelling, abscess and simple nephrosis were the other changes found.

In our patient the outstanding renal pathologic features were the large white kidneys, swelling and congestion of many glomeruli, numerous wire-loops in the glomerular capillaries, some interstitial sclerosis, crescent formation, atrophic and dilated tubules with hyaline and eosinophilic casts, focal areas of fibrosis and occasional intimal thickening of the small arterioles and middle-sized arteries. Fat stain showed scattered granules of red-staining material in glomerular cells, in the tubular epithelium and occasionally in hyaline casts.

Another important pathologic finding in this patient was the periarterial fibrosis in the spleen. Klemperer, Pollack and Baehr¹⁴ were of the opinion that the periarterial sclerosis found in nearly every case is so arresting that it must be considered specific. Kaiser,¹⁵ however, has shown that these lesions are not specific for lupus erythematosus, and occur in other widely dissociated diseases. He found periarterial

fibrosis of the spleen in 3.2 per cent of his control series and in approximately 85 per cent of the proven cases of lupus erythematosus. His conclusions, while against the specificity of this lesion, do not oppose its use as a positive diagnostic finding when used in conjunction with the clinical history and other pathologic findings.

COMMENTS

The *sine lupo* element of this disease picture was first stressed by Gross and Friedberg¹ in 1936. In their analysis of forty-seven cases (previously reviewed by Baehr, Klemperer and Schiffrin in 1935¹⁰) of non-bacterial thrombotic endocarditis they found seven cases, all women, which very closely resembled both the atypical verrucous endocarditis of Libman and Sacks¹⁶ as well as disseminatus lupus erythematosus, except that no skin lesions were found.

Keil in 1940² established his criteria of *sine lupo* in the following three categories: (1) Rheumatoid arthritis with sensitivity to sunlight and involvement of the kidneys and serous membranes;¹⁷ (2) febrile thrombocytic purpura with negative blood culture and renal involvement;¹⁸ (3) polyserositis with widespread involvement of other systems including the kidneys.^{19,20}

Rose and Pillsbury consider the lupus erythematosus disseminatus *sine lupo* diagnosis in the presence of fever, leukopenia, petechia or purpura, arthralgia, endocarditis, pericarditis, pleural effusion, renal injury and sterile blood cultures.

Friedberg, Gross and Wallach¹⁹ in 1936 described four cases of lupus erythematosus disseminatus *sine lupo* characterized by onset of acute polyarthritis, pleuritis, pericarditis and negative blood cultures. The fever was prolonged and all four patients showed evidence of nephritis. Only one revealed any evidence of renal insufficiency. Myocardial insufficiency was not a clinical feature.

It was previously thought that toxic products originated in the skin and were then dispersed throughout the internal

organs, giving the pathologic changes of disseminated lupus. However, numerous cases of disseminated lupus were reported in which the visceral symptoms antedated cutaneous manifestations by varying periods. In addition, very often in terminal cases of this disease the eruption disappeared entirely.¹⁷ In Stickney and Keith's⁵ paper in 1940, two patients of fifteen had albuminuria before cutaneous symptoms, suggesting that the skin lesion does not necessarily appear before dissemination of the disease.

The other unusual feature of this case was the presence of a nephrotic syndrome associated with hypertension and azotemia. Brooks²¹ in 1895 described a case of disseminated lupus erythematosus in a thirty-three year old woman whose kidneys postmortem showed "soft white swelling." In Stickney and Keith's⁵ series of fifteen cases there was one that had some evidence of subacute or early chronic glomerular nephritis. In all of their fifteen cases the kidneys were either normal or greater than normal in weight. Keil² in 1940 stated that he encountered several instances of disseminated lupus erythematosus in which the clinical features simulated the nephrotic phase of glomerulonephritis with moderate elevation of blood pressure.

Lupus erythematosus disseminatus has been considered a systemic disease of unknown etiology, with clinical and laboratory findings that indicate involvement of many organs. The intensity of signs and symptoms in any one system is unpredictable. The skin may be spared occasionally, as in our case, thus making the term lupus erythematosus, which implies a skin disease, a misnomer. Likewise, the term lupus is inaccurate since the tuberculous etiology has been disproven. The endocardium may be spared and therefore every case need not have a Libman-Sacks component.

The general pathologic findings are as variable as the clinical manifestations. The widespread collagen involvement with focal distribution is not specific since it also occurs in other systemic diseases such as rheumatic

fever, periarteritis nodosa, scleroderma and dermatomyositis. The wire looping of the glomerular capillary and the periarterial fibrosis ("onion peel") of the spleen has been mentioned. The renal pathologic picture is non-specific and diverse, ranging from minimal to widespread damage.

Most clinical entities are established and authenticated by pathology; however, this does not hold true for lupus erythematosus disseminatus because the pathologic changes are non-specific. Therefore, the diagnosis can be determined only by correlation of the various system involvements and the exclusion of other symptom-complexes. As Reifstein²² states the clinical features together have a fairly characteristic grouping but, considered individually, show much variation. The above views are in keeping with the teachings of the late Soma Weiss.^{23,24}

The clinical diagnosis of lupus erythematosus disseminatus sine lupo in our patient was made because of the long-standing and remittent arthritis, prolonged intermittent fever with sterile blood cultures, leukopenia and anemia, generalized lymphadenopathy, systolic and questionable diastolic murmur, polyserositis and a gradual downhill course. This entire symptom-complex was superimposed upon what resembled the nephrotic phase of chronic glomerulonephritis. The renal picture with hypertension and azotemia was unusual.

The clinical impression was strengthened by the pathologic findings of polyserositis, atypical verrucous endocarditis, lymphadenopathy, large white kidney with wire looping, periarterial fibrosis of the spleen and the absence of lesions associated with rheumatic fever.

SUMMARY

1. A case of lupus erythematosus disseminatus, without skin manifestations (sine lupo), is presented and the autopsy findings are described.
2. Other interesting features of the case are the nephrotic component, hypertension and renal insufficiency.

3. The literature is reviewed in reference to these unusual features.

4. The relationship of the clinical picture to the pathologic condition in this syndrome is discussed.

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Hemolytic Staphylococcus Albus Bacteremia and Pericarditis Treated with Sodium Salt of Penicillin and Penicillin in Beeswax and Peanut Oil

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USE of the sulfonamide drugs for the past few years in treatment of staphylococcic bacteremia and staphylococcic infections has proven ineffective for the most part. However, since the advent and development of penicillin preparations, prognosis in these diseases has been immeasurably improved. The drug has proved itself of inestimable value in the prevention and active therapy of metastatic abscesses which are a constant threat in staphylococcic bacteremia. Penicillin suspended in peanut oil and beeswax, as developed by Romansky, is finding progressively wider application. He has demonstrated that adequate and prolonged concentrations of the drug may be maintained in the blood serum after a single injection of 300,000 units contained in 1 cc. of the mixture, using the intramuscular route. The efficacy of this preparation in the treatment of gonorrhea and syphilis by single daily injections has been established. Several cures of subacute bacterial endocarditis have been reported during use of penicillin-beeswax-oil mixture. However, no reports of its use in acute staphylococcic bacteremia have been noted by the author. The therapeutic problem in this type of infection is to maintain adequate serum concentrations of the drug to render the blood stream sterile as quickly as possible, thereby preventing development of metastatic abscesses, purulent pericarditis and/or other possibly fatal complications of the disease. This desired serum concentration,

of course, will vary with the susceptibility of the organism to the drug.

It is the purpose of this paper to report a case of a patient with acute staphylococcal bacteremia who developed metastatic abscesses and pericarditis with congestive heart failure. He was successfully treated by the use of both the sodium salt of penicillin and penicillin in beeswax and peanut oil. At the time of the patient's illness a method for determination of serum penicillin concentration was not available in this hospital. It was thought, therefore, that both dosage forms of the drug should be used in order to produce promptly and maintain a serum penicillin level well above the theoretical concentration to which the organism was susceptible.

CASE REPORT

A twenty-three year old, white soldier was admitted to the Station Hospital, Camp Hood, Texas, September 17, 1946, complaining of severe pain in the right hip. Seven days prior to admission he had noted a "catch" in his hip which progressed over the next few days to a steady, dull ache with radiation to the right knee on weight bearing. This was followed by the occurrence of chills, fever and sweats each night until his admission. He had superimposed generalized aches and pains, weakness, anorexia and fatigue.

The patient had lost about 30 pounds over a three-year period of time but had had no accompanying fatigue, nervousness or asthenia. He had gonorrheal urethritis in 1942 and 1943 and had had urethral sounds passed in 1943 about

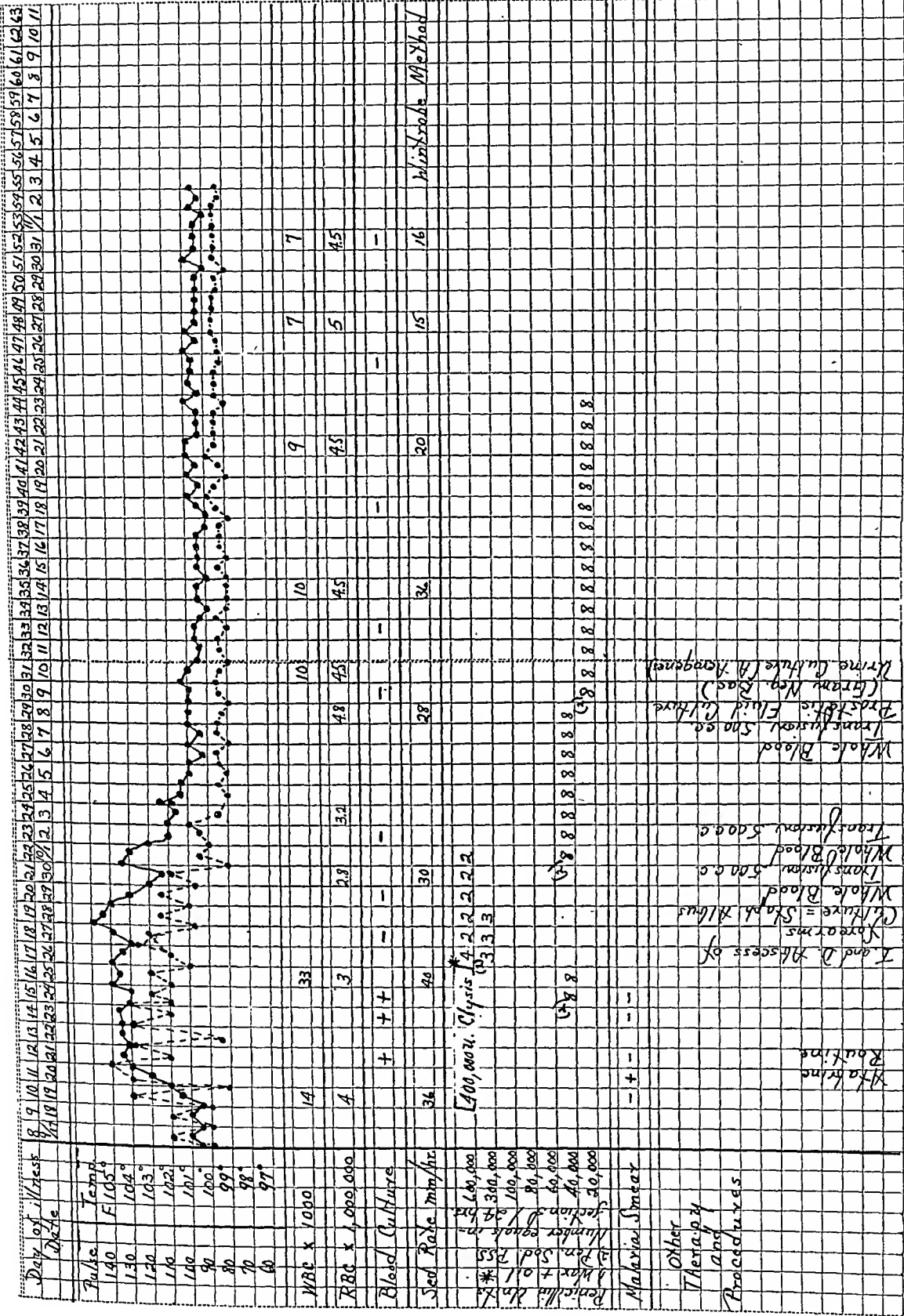


Fig. 1. The patient's clinical course in the hospital.

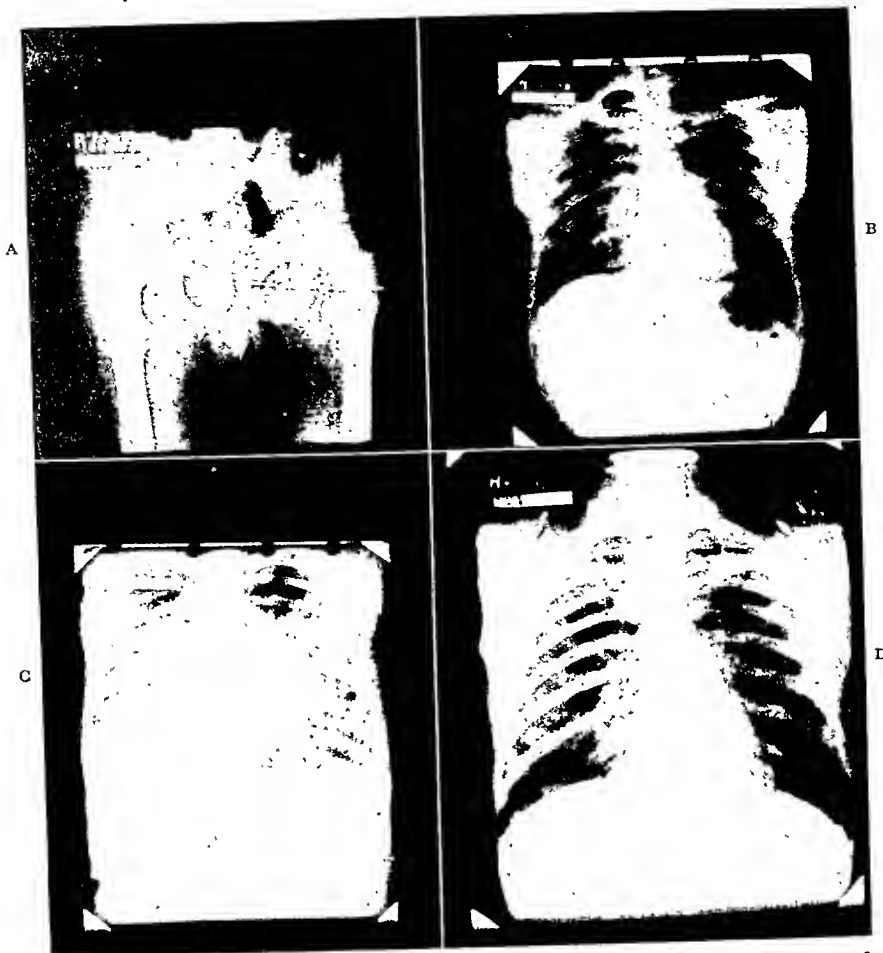


FIG. 2. A, the metallic rings encircling the femur may be seen. No evidence of osseous pathologic change. B, normal except for the slight mitral configuration. C, film during episode of congestive failure. Heart shadow is somewhat enlarged and there is some "straightening" of the left border; there is evidence of congestive phenomena in the lung fields. D, film following recovery; a nearly normal configuration with the exception of some prominence of the pulmonary conus segment.

four months following the second episode of urethritis. There was a history of mild, chronic alcoholism. The family history was non-contributory. His past medical history disclosed that a compound fracture of the proximal third of his right femur had occurred at the age of nine years. This was treated by open reduction and surgical "wiring."

Physical examination revealed a chronically ill patient who had a temperature of 99°F., pulse rate of 110 per minute, respiratory rate of 18 and blood pressure of 110/60. There was moderate pallor. The heart and lungs were clinically normal. Equivocal tenderness over a large surgical scar on the lateral aspect of the right leg was noted.

Laboratory examination revealed the following: Blood: hemoglobin, 13 Gm.; leukocyte

count, 14,000 per cu. mm.; polymorphonuclears, 88 per cent; lymphocytes, 12 per cent. Sedimentation rate, 34 mm. in one hour. Kahn test, negative; a blood smear (thick) for malarial parasites, negative. Urinalysis: a trace of albumin and 8 to 10 leukocytes per high power field. An electrocardiogram revealed only sinus tachycardia. X-ray film of the right hip and proximal femur disclosed an old, well healed fracture through the proximal one-third of the shaft of the right femur. Two metal wire loops encircled the femur at this site.

For the first two days following the patient's admission no definite diagnosis was reached and he began to manifest a high, spiking temperature. He was treated with only the usual analgesics. On September 20, 1946, a blood smear was reported positive for *Plasmodium*

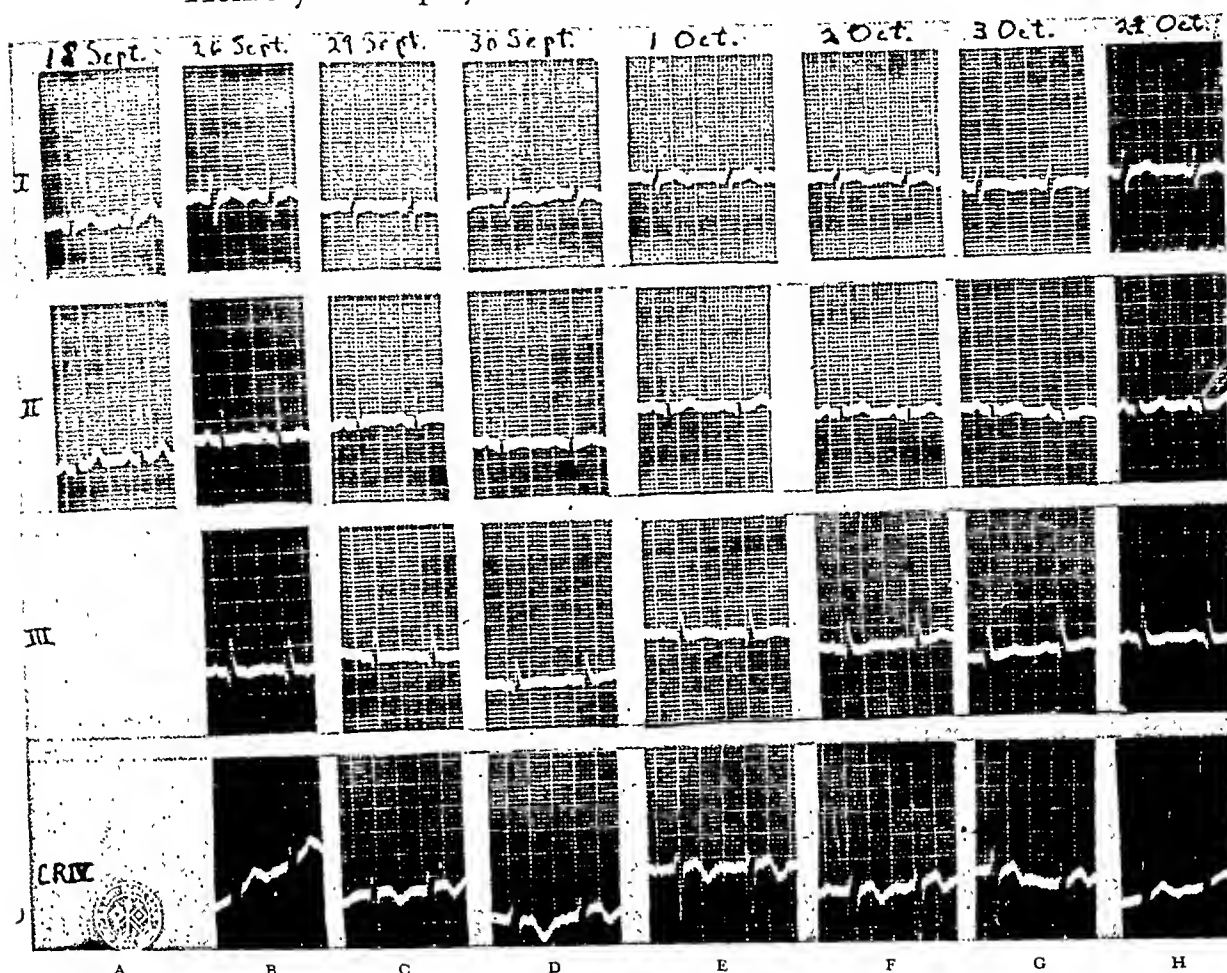


FIG. 3. A, leads I and II normal. B, there is slight widening of the QRS complexes and flattening of T_2 . T_3 is inverted. C, there is decreased voltage of all the complexes, flattening of T_1 , T_2 and T_3 and deep inversion of T_4 . S_1 has become prominent. D, further decrease in voltage of all the complexes is noted. T_1 and T_2 are diphasic and there is deeper inversion of T_4 . E, F and G, amplitude of all complexes is slowly increasing and the T waves are returning to a more normal configuration. H, this tracing is within normal limits as have been all subsequent tracings. There were no significant S-T segment changes noted in the series presumably because the pericarditis was rather slow in onset.

vivax and routine atabrine therapy was instituted. He did not improve, the temperature was unaffected and he continued to complain of pain in his right hip and proximal femur. On September 23, 1946, swollen, hot, edematous areas were noted on the dorsal aspect of both forearms which rapidly progressed to a fluctuant state. On September 24, 1946, a blood culture was reported positive for hemolytic staphylococcus albus.

Laboratory findings revealed the following: Blood: hemoglobin, 11 gm.; erythrocytes, 3,000,000; leukocytes, 33,100; polymorphonuclears, 92 per cent; lymphocytes, 8 per cent. X-ray films of the forearms showed no bone abnormality. A film of the chest disclosed singular prominence of the pulmonary artery conus segment. Blood urea nitrogen was 14 mg.

per cent and the carbon dioxide combining power was 68.3 volumes per cent.

Penicillin therapy was instituted using 40,000 Oxford units of the sodium salt intramuscularly. Incision and drainage of the forearm abscesses was accomplished and a large quantity of thick, purulent material was evacuated. Culture of the pus revealed Staphylococcus albus. Sensitivity to penicillin, streptomycin and sulfadiazine were tested by Levine's modification of the technic. The organism was found to be inhibited *in vitro* by penicillin concentrations of 0.40 units per 100 cc. and by streptomycin concentrations of 14.0 micrograms per 100 cc. It was not affected by sulfadiazine.

The veins of the arms were inaccessible because of gross infection and so a continuous hypodermoclysis of normal saline, 1,000 cc. with

400,000 units of penicillin sodium every eight hours, was given. Penicillin in beeswax and peanut oil was started using the technic of preparation and injection described by Geiger and Goerner. The 40,000 unit dosage of penicillin sodium was discontinued September 25, 1946, and the penicillin-beeswax-oil mixture was begun and continued for five days, using a dosage of 600,000 units intramuscularly every six hours for four doses and then 600,000 units every twelve hours. Two subsequent blood cultures were positive as seen on the clinical chart. (Fig. 1.) An electrocardiogram on September 26, 1946, disclosed a decrease in the amplitude of the T waves in all leads and slightly decreased voltage of all complexes.

On September 28, 1946, the patient became progressively dyspneic and orthopnea developed over a twelve-hour period of time. The neck veins became distended and the liver could be palpated two finger breadths below the right costal margin. It was acutely tender and its edge was rounded. The lung fields at first showed dry inspiratory and expiratory râles which rapidly became moist and bubbling in type. The point of maximum impulse of the cardiac thrust was in the fifth interspace 12 cm. to the left of the mid-sternal line. A gallop rhythm was present. The apical rate was 130 per minute. Paradoxical pulse was not present. A friction rub, best heard at the end of expiration, was noted and was interpreted as being pericardial in origin. A 3 plus pitting edema of the presacral area was demonstrated. The blood pressure was 130/90.

Diagnosis of acute pericarditis with right and left ventricular failure was made. The electrocardiogram disclosed low voltage of all the complexes, flattening of the T waves in the classical leads and definite inversion of T₄. A chest x-ray film demonstrated definite increase in the size of the cardiac shadow and the mitral configuration was still present. (Figs. 2 and 3.)

The patient was treated with morphine sulfate, rapid digitalization using intravenous digifoline, and 1 cc. of mercupurin was given intravenously. With other supportive therapy, the patient again became well compensated in thirty-six hours and was placed on a maintenance dose of digitalis by mouth. All clinical signs of congestive failure disappeared and subsequent chest x-ray films showed a more normal cardiac silhouette. The electrocardiogram gradually returned to normal limits. The patient continued for many days to complain of pain in

his right hip and femur but this finally disappeared. X-ray films of the hip joint, femur and knee failed to disclose any evidence of an osseous pathologic lesion.

The patient's subsequent clinical course was uneventful. The friction rub was no longer audible on October 4, 1946. The patient finally became afebrile October 21, 1946, and has continued so. The penicillin dosage was gradually reduced and finally discontinued as indicated on the clinical chart. There were no ill effects and all subsequent blood cultures have been negative. The patient has returned to duty, gained weight, has no complaints and appears in good health three months after the onset of illness.

COMMENTS

Because of the high mortality of patients with staphylococcic bacteremia complicated by metastatic abscesses and pericarditis, this patient's case was believed to be worthy of report. Use of penicillin in beeswax and peanut oil to produce and maintain a high serum concentration of the drug in acute overwhelming infections is thought to be worthy of further trial in selected cases. Sensitivity determinations should be carried out as well as serum penicillin concentrations whenever possible.

The focus of this patient's bacteremia was never established. Because of the roentgenographic mitral configuration, the possibility of chronic mitral valvulitis with endocarditis was entertained. However, in the absence of a suggestive history and a significant cardiac murmur this conjecture was discarded. The urinary tract did not seem a likely source. The history of a compound fracture of the right femur at the age of nine years coupled with the intense pain accompanying this illness strongly suggests the diagnosis of a chronic, dormant, low grade osteomyelitis of the femur reactivated during a period of general lowered resistance and a malarial parasitemia. This possibility, unfortunately, was not proven.

The development of acute pericarditis and congestive heart failure leads one to believe that the infecting organism had involved the pericardium and epicardium.

The clinical picture and electrocardiographic changes provide unequivocal evidence of myocardial involvement by the inflammatory process. It was believed that the high constant serum penicillin concentrations prevented occurrence of a purulent pericarditis. At no time did it seem clinically feasible to perform pericardial paracentesis; therefore, this opinion must remain conjectural. This patient's rapid recovery from a staphylococcal bacteremia with metastatic abscesses and pericarditis and the paucity of reports of patients treated in the manner outlined, makes this case significant.

CONCLUSIONS

(1) A case of staphylococcus albus bacteremia complicated by peripheral metastatic abscesses of the forearm and acute pericarditis accompanied by congestive heart failure is described. Complete recovery was accomplished using penicillin sodium in conjunction with penicillin in beeswax and peanut oil.

(2) Penicillin sodium was used subcutaneously and intramuscularly and penicillin in beeswax and peanut oil was given intramuscularly. In the opinion of the author the high penicillin concentration

was responsible for the cure of the infection and prevention of development of a purulent pericarditis and other metastatic abscesses.

(3) The treatment followed seems worthy of further trial in similar cases requiring a high serum penicillin concentration because of massive infection and/or a resistant organism.

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Gladwyne, Pennsylvania

Congenital Dextrocardia Complicated by Hypertension, Coronary Artery Disease and Myocardial Infarction*

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Congenital dextrocardia associated with coronary artery disease is rare as judged by reports in the literature. Crawford and Warren¹ described a fifty-eight year old male who had congenital dextrocardia, a history of severe prolonged substernal pain associated with numbness in the right arm and the anginal syndrome upon effort. An electrocardiogram taken several months later and interpreted with the arm lead wires reversed was consistent with posterior wall infarction. Manchester and White² reported the case of a sixty-seven year old male with dextrocardia complicated by hypertension, coronary artery disease and the anginal syndrome. An electrocardiogram showed an abnormal T₁, prominent Q₂ and Q₃ and inverted T₄. There were no QRS changes in a single precordial lead. Geeslin and Tyler³ took serial electrocardiograms on a forty-three year old male with dextrocardia following myocardial infarction. The changes were typical of anterior wall infarction. CF₂, CF₃ and CF₄ of the precordial leads were taken over the right side of the chest. The limb leads were interpreted with the arm lead wires reversed. Cain⁴ found the electrocardiogram of a thirty-three year old male with congenital dextrocardia and the anginal syndrome to be normal except for left axis deviation. Interpretation was made with the arm lead wires reversed. Ogaard, Voorhies, Bureh and Cordill⁵

recorded electrocardiograms on seven persons with congenital dextrocardia. Multiple precordial leads of the CF series, when taken over the right side of the chest, were found to be comparable to precordial leads from the left side of the chest when the heart is in normal position. One child, age fourteen years, showed T wave changes over the right ventricle, and one adult subject with hypertension showed T wave changes in each of the precordial leads. Q waves present in positions 5 and 6 in three subjects were of small amplitude; the largest was only 2.4 mm. in depth.

That the electrocardiogram in congenital dextrocardia can be interpreted by the usual criteria if viewed or taken with the arm lead wires reversed is further substantiated by the instance reported by Wil-lius⁶ of a fifty-nine year old male with hypertension. The electrocardiogram disclosed the RS-T segment and T wave deflection in opposite direction to the QRS complex in lead I representing the pattern of "left ventricular strain."

CASE REPORT

D. S. S., a seventy-three year old white married male farmer, was admitted to Duke Hospital on May 30, 1947, because of four episodes of substernal pain radiating to the right arm during the preceding two weeks. His past history was interesting in that he had had pneumonia in 1937 and was hospitalized for two

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months. He was informed at that time that his heart was in the right side of his chest. His health remained excellent until two weeks before admission when, while plowing, he developed sudden, severe, substernal pain with radiation to the right arm. Plowing was continued until the pain became so severe that he was forced to sit down; the pain lasted approximately one hour and was associated with sweating. The following day while walking home from town, a similar episode of pain developed which was partially relieved by rest. He continued home but was forced to stop several times because of exacerbations of the pain. Upon arriving home his physician administered a hypodermic and prescribed some capsules which relieved his pain. Physical activity was limited upon the advice of his physician and no further episodes of pain were encountered during the following week.

Six days before admission while sitting in a chair at home, he developed his most severe episode of substernal pain which was accompanied by nausea, vomiting and sweating. The pain lasted one hour until relief was obtained from a hypodermic. He then remained in bed until his admission to the hospital. Substernal pain returned on only one occasion, the night before admission; relief was obtained immediately by dissolving nitroglycerin beneath his tongue.

The temperature was 37.4°C., the pulse rate was 68 beats per minute and respirations were 20 per minute. Blood pressure was 128 mm. Hg systolic and 70 mm. Hg diastolic. Examination revealed a well developed and well nourished white male who appeared younger than his stated age of seventy-three years. Eyes, ears, nose, mouth and throat showed only mild sclerotic changes in the optic fundi; the two remaining teeth were carious and the tonsils were moderately enlarged. There was no distention of the neck veins. The lungs were clear. Examination of the heart disclosed the point of maximal impulse 8 cm. to the right of the mid-sternal line in the fifth interspace at the mid-clavicular line. The rhythm was regular. The sounds were of normal intensity but the second sound at the base was louder to the left than to the right of the sternum. A soft systolic murmur was heard at the apex. No masses or organs were felt in the abdomen and the liver could not be percussed with certainty. There were no abnormalities of the extremities and the neurologic system was intact.



FIG. 1. Teleroentgenogram showing the heart and gas bubble in the stomach on the right.

Laboratory data were as follows: Hemoglobin was 14.6 Gm.; red blood count, 4,777,000 cells per cu. mm.; white blood count, 7,100 cells per cu. mm. with 74 per cent polymorphonuclear leukocytes. The sedimentation rate was 5 mm. in one hour corrected (Wintrobe). The Kline and Mazzini reactions were negative. The blood non-protein nitrogen was 42 mg. per 100 cc.; blood urea nitrogen was 19.3 mg. per 100 cc., giving a urea ratio of 45.9. The van den Bergh test showed no elevation. Serum cholesterol was 250 mg. per 100 cc. The kidney function, as measured by the phenolsulfonphthalein excretion test, revealed 73 per cent excretion of the dye in two hours with 40 per cent excreted in the first half hour. The urinalysis was normal. A teleroentgenogram (Fig. 1) showed the heart to be enlarged to the right and the aorta was elongated and tortuous. The lungs presented increased perivascular markings and thickening of the pleura at the left apex. The diaphragms were clear and the gas bubble in the stomach was on the right. The findings were interpreted as consistent with congenital dextrocardia and situs inversus viscerum.

The electrocardiogram (Fig. 2) showed normal sinus rhythm at a rate of 76 per minute, a P-R interval of 0.19 seconds and a QRS interval of 0.12 seconds. Inversion of P₁ was present with the arm lead wires in normal position. When the arm lead wires were reversed, S₁ and S₂ were widened and slurred. T₁ and T₂ were upright and T₃ inverted. Precordial leads, V₁ through V₆, taken over the right side of the

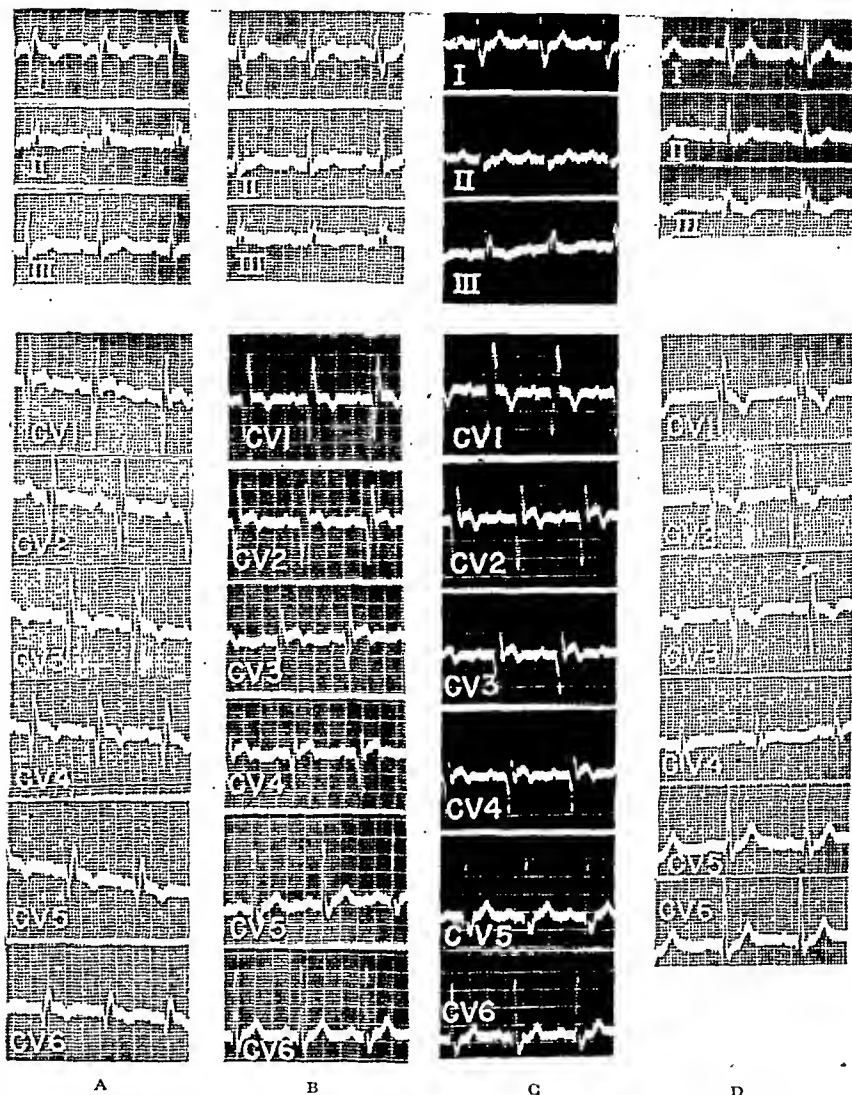


FIG. 2. A, electrocardiogram taken on admission with the arm wires correctly placed and the precordial leads taken over the left side of the chest. B, record taken the same day with the arm lead wires reversed and the precordial leads taken over the right side of the chest. C, repeat of the record five days later with the arm lead wires reversed and the precordial leads taken over the right side of the chest. D, record taken one month later.

chest showed deep Q_1 , Q_2 , Q_3 and Q_4 ; T_1 was inverted; T_2 , T_3 and T_4 were diphasic; T_5 and T_6 were upright. There was minimal elevation of the RS-T segments in positions 2 and 3. The findings were considered to be consistent with congenital dextrocardia complicated by antero-septal infarction. Precordial leads taken over the left side of the chest showed a difference in tracings from position one and two while the remainder of the leads resembled those taken from position two except for a difference in voltage. A repeat of the electrocardiogram five days later revealed no significant change in the limb leads. In the precordial leads T_1 was more deeply inverted; the RS-T segment in lead II was less elevated with T_2 more inverted; T_3 and

T_4 showed a slight increase in the depth of late inversion.

The patient remained in the hospital for fifteen days at bed rest and was afebrile during this period. There was no change in his blood pressure and no further episodes of pain were noted. During the first six hospital days he received 30 mg. of papaverine hydrochloride every four hours.

The sedimentation rates repeated on the sixth, tenth and thirteenth hospital days were 22, 20 and 30 mm. in one hour corrected (Wintrobe), respectively. The white blood counts repeated on the same hospital days were 8,700, 8,000 and 8,200 cells per cu. mm. On the fifteenth hospital day he was discharged to

lead a bed-chair existence with bathroom privileges for one month and then to resume gradually a program of limited activity.

The patient was seen again on July 10, 1947. His course at home had been uneventful. During the preceding week he had had one episode of substernal pain, related to effort, which had lasted about five minutes but which was promptly relieved by rest. On re-examination his blood pressure was 150 mm. Hg systolic and 100 mm. Hg diastolic. The remainder of the physical examination was unchanged. An electrocardiogram showed no change in the limb leads. In the precordial leads T_1 was more inverted; the RS-T segments in leads II and III were isoelectric with deeper inversion of T_2 and T_3 ; T_4 , T_5 and T_6 were slightly more upright. X-rays of the gallbladder revealed rather poor concentration of the dye but contraction was satisfactory after the fatty meal. No stones were seen. The Weltmann coagulation band was 3 and the sedimentation rate was 19 mm. per hour (Westergren).

SUMMARY

The case record of a seventy-three year old man with congenital dextrocardia and situs inversus viscerum complicated by hypertension, coronary artery disease and myocardial infarction is presented. Electrocardiographic recordings of the limb leads, with and without reversal of the arm lead wires, and of the precordial leads of the V series derived from both right and left chest areas are presented. In this instance the electrocardiographic findings in pre-

cordial leads taken over the right chest point to fresh antero-septal infarction; those leads recorded from the left chest were not informative. This serves to emphasize the fact that precordial leads should be recorded from the right side of the chest rather than the left in order that the exploring precordial electrode may overlies the area of cardiac damage, and thus manifest maximal changes in the electrocardiogram. We agree that the electrocardiogram may best be interpreted by application of the usual criteria to the limb leads taken with the arm lead wires reversed although in this case the limb leads yielded no information of diagnostic significance.

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Bromsulfalein Reaction^{*}

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SINCE the development of the bromsulfalein liver function test by Rosenthal and White in 1925, serious reactions to bromsulfalein (phenoltetrabromphthalein) have been so rare that we can find no reports in medical literature of their occurrence. That such reactions may occur is shown by the following case report:

CASE REPORT

M. M., a thirty-five year old housewife, was admitted to the Mary Hitchcock Memorial Hospital on December 19, 1946, for evaluation of recent weight loss and allergic reactions. She had been well until March, 1942 when she was hospitalized for a miscarriage. She made an uneventful recovery, but while still in the hospital had her first episode of bronchial asthma. Prior to this she had had no known allergies. Subsequently, she continued to have recurrent asthmatic attacks of moderate severity which were always worse in the spring and fall and immediately preceding her menses. During the three months before the present admission the attacks had become increasingly severe. Previous skin tests showed multiple sensitivities to food, dust and animal furs, but not to pollens. During the six weeks before admission she had become increasingly weak, easily fatigued and had lost 20 pounds. Her past history and family history were essentially negative. There was no family history of allergy or tuberculosis. Systemic review was non-contributory.

Physical examination revealed a small, thin, pale female. She weighed 85 pounds and was 61 inches tall. The blood pressure was 125 systolic and 85 diastolic. The radial pulse was 80 and the oral temperature was 99°F. The mucous membranes of the nose were swollen. There were wheezes and rhonchi throughout both lungs. The expiratory phase was prolonged. The liver edge, felt at the level of the umbilicus, was sharp, firm and nontender. All other physical findings were normal.

Examination of the urine was negative. The hemoglobin was 15 Gm. (oxyhemoglobin—Klett Sommerson) and red blood cell count was 4,880,000. The white blood cell count was 5,200 with 40 per cent segmented neutrophils, 51 per cent lymphocytes and 9 per cent eosinophils. The blood serologic test for syphilis by the Mazzini method was negative. X-ray of the chest was negative. An excretory urogram was normal. Two sputum specimens were negative for acid-fast bacilli, and the first and second strength tuberculin tests (P.P.D.) were negative. The non-protein nitrogen was 27 mg. per cent; the total serum protein was 5.2 Gm. per cent, with 3.4 Gm. per cent albumin and 1.8 Gm. per cent globulin. The serum cholesterol was 192 mg. per cent. The basal metabolic rate was -2 per cent and -6 per cent. Direct examination and culture of the stool were negative for pathogens.

An extensive allergy investigation revealed multiple sensitivities by the skin test method in all series, with most marked reactions to horse serum 1:100, beef 5,000 units per cc., pork 5,000 units per cc. and lamb 5,000 units per cc.

Because of the hepatomegaly, a study of liver function was initiated. The cephalin flocculation test was negative. The prothrombin time was 15.4 seconds with a control of 15.5 seconds (98 per cent of mean normal).

Bromsulfalein, 193 mg., (representing 5 mg. per Kg.) was given intravenously in approximately one minute. One minute later the patient suddenly became extremely apprehensive and sat forward gasping for breath. Breathing became increasingly difficult and labored; marked cyanosis appeared and the patient lost consciousness. Because she appeared in extremis, 1 cc. of epinephrine hydrochloride 1:1,000 was given intravenously. As there was no response 0.25 Gm. of aminophylline was given intravenously. Her face became ashen and the dependent parts of the body became deeply cyanotic; the veins of the arms and the neck were distended. Respirations were rapid and

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shallow. The same dose of aminophylline was repeated intravenously and an oxygen mask was applied. At this time the patient became completely apneic and remained so for three minutes. Artificial respiration was administered and oxygen therapy was continued. Spontaneous breathing began again and was accompanied by a severe, generalized clonic convulsion. A mixture of oxygen and helium was then given by mask and 30 Gm. of sodium succinate¹ were given intravenously. Following this, the patient began to have transitory periods of improved color alternating with periods of marked cyanosis. Gradually the patient's color improved; her respirations became normal and she returned to consciousness. The entire episode lasted approximately one hour. There was no recurrence, and the patient stated that she felt very well during the remainder of her hospitalization. Following the acute episode, her lungs remained clear and she was entirely asymptomatic. No further studies were made.

She was discharged six days later on a modified elimination diet with a supplementary synthetic protein preparation. Desensitization was considered impractical in view of the multiplicity and severity of her sensitivities.

COMMENT

Before reviewing the literature on bromsulfalein it is essential to acknowledge that the reaction just described may not have been entirely due to bromsulfalein. The 1 cc. of epinephrine hydrochloride which was given intravenously may have been responsible for the events which took place subsequent to its injection. That the patient survived this dose of epinephrine is in itself remarkable.² Aminophylline given intravenously also may account for some of the events which transpired as serious reactions and deaths³ have been reported from its use. The epinephrine and aminophylline, however, were administered only when the patient appeared in extremis.

Because of the extreme severity of this reaction to the intravenous administration of bromsulfalein in an individual with multiple allergies and because we were not aware of a similar reaction to this drug, a search of the literature on this subject was made.

Phenoltetrachlorophthalein was first studied pharmacologically by Abel and Rowntree⁴ in 1909. It was found by them to be non-toxic when administered intravenously and to be excreted almost entirely by the liver. A test for hepatic function using this substance was first outlined in 1913 by investigators at the Johns Hopkins Medical School.^{5,6} Phenoltetrachlorophthalein, however, had certain disadvantages. Following considerable investigation by Rosenthal⁷ and Rosenthal and White,⁸ phenoltetrabromophthalein (bromsulfalein) was found to be ideal for liver function studies. The toxicity of this substance was found to be very low. When dogs were injected with more than 100 mg. per Kg., death occurred in 50 per cent of the animals, either at once with convulsion or within two hours preceded by chills and weakness; and in one dog, 50 mg. per Kg. was found to be fatal in four hours. At autopsy no gross lesions were found and by microscopic studies the only finding was diffuse enteritis.

Although the literature is replete with papers concerning the use of bromsulfalein as a test of liver function, no reports of its toxicity have appeared since the original work.

Capps⁹ observed the results of as many as 7,000 tests a month in Italy during the war. Ingelfinger¹⁰ is using massive doses (up to 800 mg.) of the dye intravenously in his studies of hepatic circulation. Neither of them has observed a reaction as severe as the one described. Nevertheless, both mention pyrogenic reactions, sometimes associated with nausea and vomiting, six to twelve hours after the injection and lasting one to two days. They consider this to be due to impurities rather than to the dye itself. In addition, both have observed occasional mild allergic reactions associated with urticaria and asthma. Fainting has occasionally been observed, but this was considered to be on a non-specific basis.

Capps⁹ suggests that caution be used in injection of the dye. One cc. (50 mg.) of the solution is slowly injected, following which an interval of a full minute is allowed to

pass to note any untoward reactions before proceeding to inject the remainder. A total of three minutes is allowed for the injection of the full amount.

SUMMARY

A severe reaction to bromsulfalein is described. Such a reaction is extremely rare and should in no way contraindicate use of this substance. A method for injection is suggested to help prevent the type of reaction described.

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American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING
HELD IN NEW ORLEANS, JANUARY 26, 1948

QUANTITATIVE STUDY OF STERNAL MARROW MEGAKARYOCYTES. *Philip Pizzolato, M.D., New Orleans, Louisiana.* (From the Department of Pathology, Veterans Administration Hospital.)

Marrow megakaryocytes were counted by three methods: (1) Fuchs-Rosenthal counting chamber, (2) coverslip and (3) slide. The marrow was obtained from the sternum by aspiration. In the chamber method the marrow was mixed with double oxalate and diluted with 1 per cent acetic acid as for a white cell count. The total nucleated elements were obtained from the same dilution using the ordinary Levy chamber. For the other methods the marrow in the aspirating needle was used in making the preparations and stained with Wright's stain. The number of megakaryocytes observed among 5,000 nucleated cells was determined from the coverslip preparation. Using the slide method, the number of megakaryocytes and nucleated cells was observed in an area of 20 by 15 mm. The results obtained from the three procedures were transformed to the number of megakaryocytes per million nucleated cells.

In a series of ten normal individuals from eighteen to twenty-seven years of age the megakaryocytes varied from 152 to 345 per million cells using the chamber method. Megakaryocytes were determined by means of the three technics in eight pathologic states. The chamber method compared favorably with the slide method in four cases whereas the coverslip technic, which according to some observers usually gives a uniform distribution of cells, did not correspond with the other methods.

The chamber method using the Fuchs-Rosenthal counting chamber appears to be a rapid, uniform and accurate procedure for estimating the number of megakaryocytes in bone marrow.

EFFECT OF METHYL-BIS-(BETA-CHLOROETHYL)-AMINE ON HEMOPOIETIC FUNCTIONS OF THE MARROW. *William C. Levin, M.D., Galveston, Texas.* (From the Department of

Internal Medicine, University of Texas Medical School and the Hematology Clinic, John Sealy Hospital.)

Methyl-bis-(beta-chlorethyl)-amine hydrochloride was administered to fifteen patients with diagnoses of lymphoma, bronchogenic carcinoma, synovioma and other carcinomas. In most instances the patients received two or more courses of the drug. Complete studies of the peripheral blood were made every one to three days and serial examinations of the bone marrow were made during and following administration of the nitrogen mustard.

In all but three instances there were significant changes apparent in either the peripheral blood or the bone marrow. Two patients who originally displayed leukemoid reactions to the primary disease reacted to the drug by a drop in the leukocyte count. Three patients showed a drop in the leukocyte count to between 3,000 and 4,000. A moderately severe leukopenia (1,500 to 3,000) became evident in three patients and there were four patients in whom the leukocyte count dropped to below 1,000. In these four patients the thrombocyte level dropped to below 100,000. The bone marrow responded by displaying a moderate to marked hypocellularity after treatment was instituted. There was a close correlation between the degree of hematocytopenia in the peripheral blood and the severity of the marrow hypocellularity. In general the severity of depression of hemopoiesis was dependent upon the amount of drug administered.

In spite of severe hematologic reactions these patients displayed few clinical manifestations of leukopenia and in most instances complete hematologic remissions apparently developed after the drug was stopped.

EVIDENCE ON THE ORIGIN OF LEIOMYOMA-OF THE SKIN OBTAINED BY PHARMASCOLOGIC STUDIES. *William J. Senter, M.D. (introduced by M. Michael, M.D.), Atlanta, Georgia.* (From the Department of Medi-

cine, Emory University School of Medicine and the Medical Service, Grady Hospital.)

A case of multiple leiomyomas of the skin is presented. The sensitivity of these tumors to cholinergic drugs and their distribution within the area supplied by the cervical sympathetic nerves is considered conclusive evidence of their origin from smooth muscle tissue of sweat glands. It is thought that this is the only case of leiomyomas of the skin in which the site of origin of the tumors was from smooth muscle tissue deposit in the skin.

NEW METHOD FOR THE SURGICAL TREATMENT OF CARCINOMA OF THE LOWER TRACHEA AND CARINA. *Osler A. Abbott, M.D., Atlanta, Georgia.* (From the Department of Surgery, Emory University, School of Medicine.)

In the handling of carcinoma of the right upper lobe orifice it has become increasingly evident that some method allowing removal of the lower lateral wall of the trachea, carina and upper medial wall of the contralateral wall of the main stem bronchus will be necessary. This is indicated both by lesions involving this area and also in order to remove adequate area of normal tissue beyond the neoplastic lesions, especially in patients in whom the right upper lobe orifice arises either in the lower tracheal wall or in close proximity to the carina.

A new method allowing removal of these areas with primary re-establishment of continuity of the breathing tube is presented. Experiences encountered in six patients with their follow-up reports to date are discussed. Considerable attention is paid to the maneuvers necessary to allow one to keep the lower trachea open for varying periods of time in repair of such defects associated with the removal of these lesions. Attention is paid to the basic experimental work of Rollin Daniel, relative to these lesions.

THE SPATIAL VECTORCARDIOGRAM IN NORMAL MAN. *John P. Conway, M.D. and James A. Cronvich, M.S., New Orleans, Louisiana.* (From the Department of Medicine and of Electrical Engineering, Tulane University, and Charity Hospital.)

The spatial vectorcardiogram is a record of the resultant manifest potentials of the heart represented as a vector function of time.

The regular tetrahedron was employed as the reference system. Einthoven's triangle was the frontal plane. The posterior electrode position was just to the left of the tip of the seventh dorsal vertebral spine. The cathode-ray oscillograph and a camera were used for recording.

The subjects were sixteen normal male medical students. Projections of the vectorcardiogram on a mid-sagittal plane and on the frontal, superior, right and left surfaces of the tetrahedron were recorded.

\hat{E} P-Loop. The axis is directed downward, slightly forward and to the left. The inclosed area faces upward, forward and to the left. Traced counterclockwise as viewed from the front it is of irregular contour.

\hat{E} QRS-Loop. The axis is directed downward, slightly forward and to the left. The inclosed area faces upward, forward and to the right. A smooth ellipse-like figure whose width is less than one-third of its length, it is traced clockwise as viewed from the front, slowly at first, faster throughout the major portion and slowly again near its terminus.

\hat{E} T-Loop. The axis is directed downward, forward and to the left. The inclosed area faces upward, forward and to the right. It is a very narrow ellipse-like figure, traced clockwise as viewed from the front, slowly in the efferent, faster in the afferent portion.

Relative axis magnitudes of the \hat{E} P-, \hat{E} QRS- and \hat{E} T-loops are 1:10:2.

RELATIONSHIP OF THE PRECORDIAL ELECTROCARDIOGRAM TO THE ELECTRICAL FIELD OF THE HEART. *Robert P. Grant, M.D., Atlanta, Georgia.* (From the Departments of Medicine and Physiology, Emory University School of Medicine.)

The ventricular deflections of the precordial leads have been assumed to be produced predominantly by that portion of the myocardium directly beneath the electrode. In order to test this concept the extent to which the precordial deflections represented projections of the spatial cardiac vectors was studied in one hundred subjects. The three dimensional characteristics of the QRS and T vectors were determined by vector analysis of potential differences measured between four remote, electrically equidistant

electrodes on the body. The distribution of positive and negative deflections and the zones of transition for the precordial QRS and T deflections at the fourth interspace and other thoracic levels were then compared with those anticipated for them from the size and direction of the spatial vectors. In addition the precordial deflections were compared with the results from an equation which defined the surface pathway of the transitional zone for a vector of any given direction at the center of a regular ellipsoidal cylinder. There was close agreement in these regards between the precordial ECG and the spatial vectors in the patients studied. Thus, for precordial leads the heart roughly resembles a single central dipole as has already been demonstrated for the limb leads. The magnitudes of the precordial deflections increased, of course, when the electrode was nearer the heart but this appeared only to magnify the anticipated direction of the deflection. In normal subjects the transitional pathway of the QRS deflection crossed the left precordium; this was less commonly true of the transitional T pathway. The more abnormal the ventricular gradient the more disparate became the pathways; in spite of this, in most abnormal patterns both the QRS and T pathways crossed the left precordium and therefore the precordial electrode positions now in general use demonstrated transitional deflections in most instances.

VENTRICULAR GRADIENT IN HYPERTHYROID CONDITIONS. *Robert B. Failey Jr., M.D. and Albert L. Hyman, M.D. (introduced by Johnson McGuire, M.D.), Cincinnati, Ohio.*

In a study of the effect of hyperthyroidism and of thyroid extract on the heart the electrocardiograms of a group of patients were analyzed by study of their ventricular gradients. These cases were of two groups, the first composed of fourteen patients with hyperthyroidism and the second of eleven normal subjects to whom 6 gr. of thyroid extract were administered daily. All patients studied were free of complicating diseases and all had electrocardiograms that were normal except for a few instances in which transient abnormalities of cardiac rhythm were noted.

In the group with hyperthyroidism all of the fourteen patients showed an increase in the magnitude of their ventricular gradient as compared with control electrocardiograms taken

after remission of the disease induced by surgery or by thiouracil. This increase averaged 39 per cent, with a range from 4 to 100 per cent. In addition seven of this group showed a significant clockwise shift in the direction of the ventricular gradient, averaging 26 degrees with a range of plus 16 to plus 48 degrees. The other seven patients in this group showed no significant shift in the direction of the gradient.

In the group receiving thyroid extract all of the eleven subjects showed an increase in magnitude of the ventricular gradient. This magnitude averaged 30 per cent with a range from 7 to 73 per cent. None of these patients showed a significant shift in the direction of the gradient.

In both groups of patients increase in heart rate was a common occurrence, and values obtained for magnitude and direction of ventricular gradients were corrected for changes in heart rate.

It is suggested that the increased magnitude of the ventricular gradient is a reflection of the increased work of the heart. It is also suggested that the shift in the direction of the gradient in the hyperthyroid group may indicate myocardial strain since this finding has been previously noted in patients with hypertension and acute glomerulonephritis.

ACQUIRED DEFECT OF THE SEPTUM INTER-VENTRICULORUM AS A SPECIAL FORM OF MYOCARDIAL RUPTURE COMPLICATING CORONARY ARTERY DISEASE WITH MYOCARDIAL INFARCTION. *Robert H. Furman, M.D. and George R. Meneely, M.D., Nashville, Tennessee. (From the Department of Internal Medicine, Vanderbilt University, School of Medicine.)*

The authors' interest in this uncommon but not rare event following myocardial infarction was stimulated by its occurrence in a patient under their observation. The literature was reviewed and fifty-four reports noted and studied. Two cases from the authors' experience are added and clinical and pathologic observations made. Septal rupture is compared to cardiac rupture in general. Twenty per cent of seventy-six cases of cardiac rupture noted in a series of 28,657 autopsies showed septal rupture. The clinical picture is that of interventricular septal defect superimposed on that of myocardial infarction. The systolic murmur is generally

loudest in the fourth or fifth interspace close to the sternum. Two patients exhibiting diastolic murmurs had large septal tears. The average interval between infarction and cardiac rupture or septal rupture was seven days. Death following cardiac rupture occurs almost always within a few hours. The duration of life following septal rupture is considerably longer. One patient lived almost five years. Twenty per cent of the patients in whom ECG studies were made showed right axis deviation and 25 per cent showed some form of block. The site of septal perforation is almost always at or near the apex, in contrast to the congenital defect which is generally at the base.

ANOXIA PRODUCES MYOCARDIAL LESIONS IN DOGS. FURTHER EVIDENCE OF THE PART PLAYED BY CAPILLARIES IN THE PATHOGENESIS OF MYOCARDIAL INJURY. *Robert G. Gale, M.D., Robert H. Furman, M.D., Janet M. Lemley, M.D., Ira T. Johnson, Jr., M.D., Thomas F. Parrish, M.D. and George R. Meneely, M.D., Nashville, Tennessee.* (From the Department of Medicine, Vanderbilt University School of Medicine.)

Previous work from this laboratory has shown that asphyxia and local ischemia adversely affect the myocardial capillaries. The present report extends these findings by demonstrating that anoxia alone can produce myocardial capillary injury.

Fifty-one dogs were used. Room air was diluted with nitrogen in large spirometers to an oxygen concentration of 5 to 10 per cent. A tracheal T cannula was inserted and the lungs ventilated with a pump using an open circuit. Arterial oxygen saturation was measured with the Van Slyke manometric apparatus and for the most part ranged from 30 to 50 per cent saturation. In successful experiments the anoxic period was usually three or four hours although some hearts showed injury in a shorter time. In some dogs electrocardiographic records were taken. Trypan blue was used in twenty-three dogs while the remaining twenty-eight did not receive it. Only twenty-five experiments were "successful" in the sense that a prolonged period of anoxia was achieved.

Striking lesions were found in the gross in eleven dogs while questionable lesions were seen in four more. Their distribution was patchy.

No large areas comparable to some obtained under asphyxia occurred. The gross changes were more striking than the microscopic except in cases of marked hemorrhagic alteration. Trypan blue is an anticoagulant and definite lesions were more frequent when it was administered, but the possibility remains that lesions with trypan blue are more readily detected.

The pathologic character of the lesions ranged from edema through protein-containing edema fluid with slight hemorrhage to marked hemorrhagic alteration. Electrocardiographic changes were rarely seen, probably due to strictly intramyocardial location of some lesions, their small size or their patchy distribution.

NODES OF CONTRACTURE IN STRIATED MUSCLE. *Janet M. Lemley, M.D. and George R. Meneely, M.D., Nashville, Tennessee.* (From the Department of Medicine of Vanderbilt University, School of Medicine.)

The usual form of contraction in striated muscle respects the architecture of the fiber and involves only the individual myofibrillar elements of the Q stripe. There is another, probably atavistic, mechanism called "Schrumpfkcontraktionen" by Exner. One of the authors in a previous work produced these *in vivo* and reported on their nature. Nodes of contracture can be produced which are localized, non-propagated, slow compared to the twitch response, reversible when the stimulus is appropriate and irreversible when the stimulus is excessive. In their reversible form they resemble morphologically normal smooth muscle contractions while in their irreversible form they are identical with Zenker's hyaline degeneration of muscle.

Evidence is presented that this form of contraction occurs in humans as myo-edema. Acutely ischemic regions of dog hearts also exhibit this phenomenon and there is suggestive evidence that it may play a part in angina pectoris and in the SFT shifts in the electrocardiogram derived from ischemic areas.

USE OF A HYPERACTIVE CAROTID SINUS AS A POSSIBLE AID IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE. *R. Bruce Logue, M.D. and Robert L. Whipple, M.D., Atlanta, Georgia.* (From the Emory University Hospital, Emory University.)

The characteristic electrocardiographic changes of myocardial infarction are prevented by the presence of left bundle branch block since the initial negativity of the left ventricle is replaced by positivity. This is due to transeptal activation of the blocked ventricle from right to left. Thus, the diagnostic changes in the QRS and T waves cannot occur. On occasion the conducting pathways are incompletely damaged so that transient or intermittent bundle branch block may occur. During the period of normal intraventricular conduction the changes due to coronary artery disease may be apparent, only to disappear with recurrence of bundle branch block. When the conducting pathways are only partially damaged, normal conduction may at times occur when the sino-auricular rate is slowed. This is presumably due to the longer refractory period of the muscle which allows the damaged tissue to recover sufficiently to conduct the excitatory process. There may be in any given individual a critical rate above which the bundle will not conduct and below which normal conduction occurs. Normal intraventricular conduction has been established in such instances by administration of ergotamine tartrate intravenously which produces reflex slowing through its sympatholytic action. It might be expected that in the presence of an irritable carotid sinus a similar result would occur. Such an example was noted in the present case in which left bundle branch block occurred with the onset of myocardial infarction. The presence of an irritable carotid sinus allowed the underlying changes associated with coronary disease to be recorded. Each of the standard and six precordial leads were taken before, during and after carotid sinus pressure and the effect of various autonomic drugs was studied.

EFFECT OF VASOCONSTRICTIVE AND HYPERVOLEMIC MEASURES UPON TETRAETHYL AMMONIUM ORTHOSTATIC HYPOTENSION. A. Ruskin, M.D. and (by invitation) H. Roosth, M.D. and H. B. Griffin, Galveston, Texas. (From the University of Texas Medical Branch.)

We have previously reported the finding of orthostatic hypertension in various clinical states in which vasodilatation seemed to play a prominent part (*Proc. Am. Fed. Clin. Research*, 3: 44, 1947). Among the conditions previously

and recently observed to be associated with orthostatic hypotension of various degrees have been acute and severe chronic anemias, other blood dyscrasias, hyperthyroidism and alcoholism. Both ephedrine and desoxycortico-sterone were observed by us to prevent in various degrees the orthostatic phenomenon.

Tetraethyl ammonium uniformly produced orthostatic hypotension in doses of 0.2 Gm. to 0.5 Gm. intravenously. In some patients we observed relative hypertension in the recumbent position, a phenomenon also often observed in clinical orthostatic hypotension. With a dose of 0.5 Gm., orthostatic syncope was common, with marked hypotension and tachycardia. The effects were less or gone within thirty minutes in the majority of cases.

Tetraethyl ammonium regularly decreased the circulating blood volume (Evans blue method). While preliminary injections of pare-
drine (30 to 60 mg.), ephedrine (50 mg.), plasma (750 to 1,000 ml.) and desoxycortico-sterone (20 to 40 mg. plus 10 gm. of NaCl) increased the blood volume, subsequent tetraethyl ammonium injections produced variable results. In some cases orthostatic hypotension and tachycardia were prevented, in others they were not. Likewise, the drops in circulating blood volume following tetraethyl ammonium were prevented in some cases, particularly by preliminary pare-
drine and plasma. As in clinical cases venous pressures and circulation times in the recumbent and upright positions were apparently not affected by "etamon" orthostatic hypotension short of syncope.

"ALBUMIN-ADDITION" TEST. F. Homburger, M.D., Edward S. McCabe, M.D., N. F. Young, M.D. and Edward C. Reifstein, Jr., M.D., New York, New York. (From the Department of Clinical Investigation, the Sloan-Kettering Institute for Cancer Research, Memorial Cancer Center.)

Intravenous administration of 75 Gm. of human albumin in normal subjects and in patients with hypoproteinemia causes a temporary rise in the concentration of albumin. Return of the albumin level to the pre-injection value is not as rapid as normal in some patients with hypoproteinemia. The significance of these differences in the rate of disappearance of the injected albumin are discussed, particularly in

relation to the various etiologic factors that lead to hypoproteinemia.

"PROTEIN-SUBTRACTION" TEST. *F. Hamburger, M.D., N. F. Young, M.D. and Edward C. Reifenstein, Jr., M.D., New York, New York.* (From the Department of Clinical Investigation, the Sloan-Kettering Institute for Cancer Research, Memorial Cancer Center.)

Removal of circulating protein by plasmapheresis in normal subjects is followed by a moderate fall in the serum protein level at twenty-four hours and by a prompt restoration to the pre-injection value or higher at forty-eight hours. In some patients with hypoproteinemia the depression of the serum protein level is considerably greater than normal at twenty-four hours, and return of the protein level to the pre-injection value is not as rapid as normal. The significance of these differences in the degree of depression and in the rate of restoration of circulating protein after acute withdrawal are discussed, particularly in relation to the various etiologic factors that lead to hypoproteinemia.

QUANTITATIVE STUDIES OF HUMAN LIVER GLYCOGEN. *Philip K. Bondy, M.D. and Walter H. Sheldon, M.D., Atlanta, Georgia.* (From the Departments of Medicine and Pathology, Emory University School of Medicine, and Grady Hospital.)

Although numerous analyses of liver glycogen in animals have been recorded, few such observations have been made in humans. It seemed desirable to determine liver glycogen concentrations in humans and to correlate these with the findings in animals. Serial human liver biopsy specimens have been obtained by needle biopsy and stained with Gomori's test for glycogen. It has been shown that the optical density of the stained slides, determined photometrically, is directly correlated with the liver glycogen content determined by the method of Good, Kramer and Somogyi. This correlation permits quantitative determination of the glycogen content of the liver by photoelectric densitometer readings from the histologic preparation.

The technic has been applied to four patients with diabetic acidosis. In three, in whom acidosis was severe, the initial glycogen content ranged from 0.20 to 0.28 per cent. After treatment the glycogen content was increased until

at seven hours it was normal (4.35 per cent). In one patient with mild acidosis the liver glycogen content before treatment was 2.30 per cent.

Three normal fasting patients have shown glycogens ranging from 2.36 to 4.25 per cent. After breakfast the glycogen content was increased. One patient fasted for thirty-six hours. Her initially normal glycogen level (3.20 per cent) decreased progressively to a low of 1.85 per cent, at which time her serum acetone level was 20 mg. per 100 ml. and her urine acetone negative.

These findings suggest that in certain respects the human liver glycogen response pattern may be somewhat different from that of the animals commonly used for experiments on carbohydrate metabolism.

GRAMICIDIN DERIVATIVES. *Godfrey E. Mann, M.D. and Otto Schales, M.D., New Orleans, Louisiana.* (From the Department of Biochemistry, Tulane University and Chemical Research Laboratory, Alton Ochsner Medical Foundation.)

Gramicidin, a potent antibiotic agent, has not been employed systemically because of its high toxicity and its hemolytic properties. A number of derivatives of this substance were prepared which were considerably less toxic and hemolytic than the starting material but retained an appreciable antibacterial activity. Some of the reagents employed for this purpose were sodium hydroxide, iodine, hydroxylamine, hydrogen chloride in glacial acetic acid and hydrogen peroxide. The reactions of gramicidin with these substances were carried out under mild conditions to avoid excess degradation of the polypeptide molecule. Hemolytic activity was measured by allowing the various derivatives to act upon a suspension of washed human red cells in isotonic saline. Progress of the hemolysis was determined periodically by a turbidimetric procedure. Bacteriostatic tests were performed by incubating standard dilutions of the test organisms with various concentrations of the derivatives and estimating turbidimetrically the concentration required to inhibit growth by 50 per cent. Toxicity data were obtained using white mice as test animals. The various derivatives had from 1 to 0.1 per cent of the toxicity of gramicidin when given intravenously. Their bacteriostatic activity was from

20 to 90 per cent of that of gramicidin. The hemolytic activity of the various gramicidin derivatives in isobacteriostatic concentrations was 7 to 20 per cent of that of the starting material. Both human and bovine plasma had an inhibitory effect on hemolytic and bacteriostatic activities of gramicidin and its derivatives. This effect is predominantly due to the globulin fraction IV-1; crystalline bovine albumin did not reduce the bacteriostatic and hemolytic properties of gramicidin and its derivatives.

SIGNIFICANCE OF RECURRENT POSITIVE BLOOD CULTURES IN PATIENTS WITH BACTEREMIA AND ENDOCARDITIS DURING THERAPY WITH PENICILLIN. *Harold L. Hirsh, M.D., Harry F. Dowling, M.D. and Jay A. Robinson, M.D., Washington, D. C.* (From the Department of Medicine, Georgetown University, School of Medicine.)

Although resistance to penicillin has been induced in strains of penicillin-sensitive bacteria *in vitro*, there are few reports on increased resistance *in vivo* during treatment.

Of fifty-five patients with endocarditis and bacteremia treated with penicillin eleven had a recurrence of a positive blood culture during therapy. In each instance the causative organisms were found to be more resistant to penicillin. In seven patients, two with staphylococcal bacteremia, three with staphylococcal endocarditis and two with *Streptococcus viridans* endocarditis, this was accompanied by a return of symptoms of active infection. The increase ranged from 4- to 2048-fold. Three strains exhibited increases on one occasion, one on two, one on three and two on four occasions. The blood penicillin concentrations were determined in six patients after the appearance of organisms with increased resistance. Since it is established that in patients with endocarditis blood levels four to eight times the *in vitro* sensitivity of the causative organisms are required, none of these patients can be considered as having had an adequate level. The dose was increased in all the patients and recovery followed in four, one died of overwhelming infection, another was ultimately cured with streptomycin and another died of debility with no evidence of active infection. In the other four patients, one each with staphylococcal and *Str. viridans* endocarditis and two with staphylococcal bac-

teremia, the bacteriologic findings were not accompanied by symptoms of active infection. The increases ranged from 2- to 4-fold. Adequate blood concentrations of penicillin were found in the two patients in whom they were determined. The dose of penicillin was continued and the patients recovered.

The significance of these bacteriologic findings is discussed. It has been observed that an occasional organism will manifest as much as an 8-fold change in sensitivity to penicillin spontaneously or as a result of the inaccuracy of the method. It is believed, however, that the increases in resistance to penicillin observed in the seven patients represent true changes in penicillin sensitivity. The significance of the increased resistance in the other four patients is unknown.

STREPTOMYCIN IN THE TREATMENT OF PERTUSSIS. *Jerome L. Kohn, M.D. and Lewis W. Wannamaker, M.D., Durham, North Carolina.* (From the Department of Medicine, Duke University.)

One hundred twenty-nine patients with pertussis were treated with streptomycin at the Willard Parker Hospital in New York City; one hundred of these were infants under one year of age. On admission, eight patients were classified as mild, ninety-six as moderate and twenty-five as severe. Streptomycin was administered by one of three routes; (1) as an aerosol, (2) intramuscularly or (3) as nose drops. Aerosol treatments were given to young infants by means of a small plastic oxygen hood. Eight patients who were considered critically ill were given hyperimmune human pertussis serum in addition to the streptomycin. There were five deaths. In the remaining patients the subsequent clinical course was judged to be good in ninety-five, fair in twenty-seven and poor in two. Skin tests employing lyophilized pertussis agglutogen were done on 123 patients. A positive reaction was obtained in eighty-two patients (66 per cent).

EFFECT OF SYMPATHECTOMY ON BLOOD VOLUME IN HYPERTENSIVE PATIENTS. *H. S. Mayerson, M.D. and W. D. Davis, M.D., New Orleans, Louisiana.* (From the Department of Physiology, Tulane University, School of Medicine and the Ochsner Clinic.)

Serial blood volume determinations were made in twenty-one patients with hypertensive vascular disease before and at intervals after sympathectomy. The follow-up period ranged from two weeks to eighteen months. In all but one patient, in whom a transthoracic approach was used, thoracolumbar sympathectomy was done. Plasma volumes were determined by the dye technic, 5 ml. of 0.5 per cent T-1824 (Evans blue) being used for injection. Optical densities were measured with the photoelectric colorimeter; dye-free plasma was used as a blank. Total circulating red cell mass was calculated from peripheral venous hematocrit and total circulating protein from the specific gravity of the plasma obtained by the falling drop method.

In this group of patients no consistent relationship between blood volume and blood pressure levels was demonstrated following operation. The most constant observation was considerable decrease in red cell mass in the early postoperative period usually accompanied by a concomitant increase in plasma volume. This was attributed to operative blood loss and was exhibited by ten of twenty patients. In some patients postoperatively there was close correlation between the blood volume changes and blood pressure response but in others there were wide divergencies. These included instances of falling blood volume and increasing blood pressure as well as the reverse.

Of the four patients who have had good blood pressure responses to operation three had high blood volumes and red cell mass values preoperatively and one was within normal range. All five patients who had poor results from sympathectomy had low circulating red cell masses and three had low total blood volumes. In general those patients with relatively advanced vascular disease tended to have low values both for circulating red cell mass and total blood volume.

INADEQUACIES OF PROPYLTHIOURACIL IN THE TREATMENT OF THYROTOXICOSIS. *Arthur B. Codington, M.D. and Philip K. Bondy, M.D., Atlanta, Georgia.* (From the Department of Medicine, Emory University, School of Medicine and the Medical Service, Grady Hospital.)

In the evaluation of the therapeutic effectiveness of propylthiouracil, certain variations of

response were encountered which are not generally appreciated. The therapeutic dose appears larger than is generally stated. Relapses have occurred after an initial response without altering the dose of propylthiouracil. Certain patients have proved totally refractory to large amounts of the drug.

Forty-five patients have been observed in fifty-two separate episodes of thyrotoxicosis. Twenty-nine of these patients with such episodes have been treated with propylthiouracil. The remainder have received thiouracil or a combination of thiouracil and propylthiouracil separately.

Propylthiouracil in a dose of 75 to 100 mg. per day has generally proved ineffective. Several patients on this dose initially made a partial response but subsequently relapsed despite unchanged dosage. On 150 mg. per day the results were improved but a significant number of patients still did not respond satisfactorily. Two patients relapsed under treatment with this dose. Of nine patients who did not respond satisfactorily to 150 mg., two did well on 200 mg., two required a dose of 250 mg. and one made a response only when the dose was increased to a level of 300 mg. One patient after being inadequately controlled on 300 to 350 mg. for five months has recently shown remarkable improvement on 400 mg. per day. Three patients must still be considered therapeutic failures despite intensive therapy with doses of propylthiouracil of 300 mg. or above. Only one instance of toxicity with propylthiouracil has been encountered, a case of leukopenia, which rapidly cleared upon stoppage of the drug.

In certain instances a beneficial effect has been shown with administration of iodides in conjunction with propylthiouracil.

SUCCESSFUL TREATMENT OF ACUTE THYROIDITIS WITH THIOURACIL. *T. Haynes Harvill, M.D., Dallas, Texas.*

Six patients with acute thyroiditis were successfully treated with thiouracil, with rapid and dramatic improvement in objective findings and subjective complaints. Diagnostic features of acute thyroiditis are enumerated. Mild granulocytopenia was encountered in one patient. This report supplements and confirms the experience of King and Rosellini who first advocated the use of thiouracil for acute thyroiditis.

INTESTINAL PARASITES IN PUERTO RICO.

Oscar Felsenfeld, M.D. and Viola Mae Young, M.S. (by invitation), San Juan, Puerto Rico. (From the Presbyterian Hospital.)

The stool specimens of 200 natives of Puerto Rico who live in San Juan or its suburbs and who came to the clinic or were admitted to the wards of the Presbyterian Hospital of San Juan for other reasons than diarrhea, were examined with the aid of a method consisting of saline and iodine smears and flotation. Parasites were present in 144. Multiple infections were numerous. The occurrence of the parasites detected with the aid of the above method was the following: *E. histolytica*, 18 per cent; *E. coli*, 31 per cent; *E. nana*, 27 per cent; *I. butchlii*, 2 per cent; *Dient. fragilis*, 0.5 per cent; *G. lamblia*, 3.5 per cent; *Ch. mesnili*, 1 per cent; *T. hominis*, 2.5 per cent; *Emb. intestinalis*, 1 per cent; *Enteromonas*, 0.5 per cent; *N. americanus*, 11 per cent; *A. lumbricoides*, 2.5 per cent; *Tr. trichiura*, 19 per cent; *Strong. stercoralis*, 0.5 per cent; *Intercapsifer*, 0.5 per cent; *Balant. coli*, 0.5 per cent; *Sch. mansoni*, 0.5 per cent. Most patients infected with helminths had a low blood hemoglobin content and eosinophilia, the latter reaching as high as 51 to 53 per cent. No connection could be found between helminthic or *E. histolytica* infections and the occurrence of target cells which are frequently present in the blood of children and pregnant women with hypochromic anemia. The *E. histolytica* strains mostly belonged to the so-called "small variety" of this organism.

VALUE OF PROCTOSCOPY IN DIAGNOSIS OF

AMEBIAS. *Spalding Schroder, M.D., Atlanta, Georgia. (From the Emory University School of Medicine.)*

From April 20, 1945, to August 8, 1945, 632 patients complaining of moderately severe diarrhea or dysentery were proctoscoped at an Overseas Army General Hospital. Adequate microscopic examination of their feces was also performed. A diagnosis of amebiasis was made in one hundred of these patients and it is these cases which furnished the material for this study.

Of the one hundred patients with amebiasis there were fifty in whom both positive proctoscopic findings and trophozoites were demonstrated. Twenty-seven patients had trophozoites of *E. histolytica* but their rectosigmoids appeared

normal to proctoscopy. The remaining twenty-three patients had negative stool examinations and rectal smears, but rectal lesions were visualized that were considered typical of amebiasis. Furthermore, these twenty-three patients responded symptomatically to routine antiamebic therapy and repeated proctoscopic examinations revealed that the lesions healed normally. It is because of these findings that demonstration of the trophozoites is not considered obligatory in establishing a diagnosis of intestinal amebiasis.

Because of the high incidence of unsuspected amebiasis and the need for greater accuracy in its diagnosis, more general use of the proctoscope is recommended.

APPLICATION OF A QUANTITATIVE GONOCOCCAL COMPLEMENT FIXATION TEST TO THE DIAGNOSIS OF ACUTE POLYARTHRITIS. *Max Michael, Jr., M.D., Atlanta, Georgia. (From the Medical Service, Lawson VA Hospital, and the Department of Medicine, Emory University School of Medicine.)*

An exact etiologic diagnosis in cases of acute polyarthritis is one of the more difficult problems encountered in medical practice. In an attempt to better classify this group of patients a quantitative gonococcal complement fixation test has been investigated. This test has fallen into disrepute in many clinics in this country principally because of the uncertainty of its specificity. Realizing the vagaries of the procedure, we have attempted to maintain caution in reaching conclusions.

The soluble antigen is prepared using a modification of the method described by Price. The choice of organism for antigen is one of trial and error. The organism chosen must have wide antigenic properties and low anticomplementary powers. It has been found using the present method that a single strain is adequate and that the use of combined antigens does not increase the sensitivity of the test. Observations made thus far may be summed up as follows: (1) The test appears to be specific for gonococcal infection. Sera from patients with various types of non-gonococcal arthritis, both acute and chronic, give negative reactions. (2) Positive results are obtained in all patients with gonococcal arthritis, however, a single negative fixation test does not rule out the presence of gonococcal infection. Serial samples must be

run for probably two months from the onset of the disease before a negative test assumes significance. (3) No characteristic antibody pattern is observed in patients with gonococcal arthritis. The pattern or height of the response appears uninfluenced by the presence or absence of gonococci in the joint fluid or whether or not chemotherapy has been administered. Furthermore, no correlation is noted with the degree of activity of the joint as evidenced by pain, swelling, fever or sedimentation rate. (4) In general once a positive test reverts to negative, activity in the joint has subsided. On the other hand, it is not uncommon to have a persistently elevated titer after all other clinical and laboratory manifestations of the disease have disappeared. The results obtained with the test in the past one and one-half years are sufficiently encouraging to warrant continued investigation.

LYMPHOGRANULOMA VENEREUM OF SUPRA-CLAVICULAR LYMPH NODES WITH MEDIASTINAL LYMPHADENOPATHY AND PERICARDITIS. *Walter H. Sheldon, M.D., Margaret Wall, M.D., John R. Slade, M.D. and Albert Heyman, M.D. Atlanta, Georgia.* (From the Departments of Pathology and Medicine, Emory University, School of Medicine, and Grady Memorial Hospital.)

Isolated cases of systemic lymphogranuloma venereum have been reported but few of them have been proven by isolation of the virus of this disease. We have studied a patient with peri-

carditis and mediastinal and supraclavicular lymphadenopathy and isolated this virus from one of the lymph nodes.

The patient was a young Negro who was admitted because of a pericardial friction rub and roentgenographic demonstration of mediastinal lymphadenopathy. The only other significant physical finding was a single large supraclavicular lymph node. Histologic examination of this node revealed pathologic changes typical of active lymphogranuloma venereum. Hyperglobulinemia, a positive Frei test and a significantly high titer of complement-fixing antibodies for lymphogranuloma venereum were demonstrated. Another supraclavicular lymph node appeared several weeks later. Histologic examination of this also showed active lymphogranuloma venereum. A virus was isolated from this lymph node by intracerebral inoculation into mice and was identified as the agent of lymphogranuloma venereum. It seems reasonable to assume that the mediastinal lymphadenopathy and the pericarditis were also caused by this agent. Thorough studies revealed no evidence of other etiology.

The patient was afebrile and did not appear ill. The pericardial friction rub subsided spontaneously but a moderate tachycardia persisted. He has been followed for three months but no further changes have been observed.

Certain facts in connection with this case deserve emphasis. The histologic picture of this disease is often diagnostic. Lymphogranuloma venereum is a systemic disease in which the presenting manifestations may not suggest venereal origin.

Editorial

Coronary Arteries as End Arteries

THE question whether the coronary arteries are end arteries has been subjected to vigorous discussion for many decades. Intense interest in this problem has been provoked not only because of its scientific importance but also because of the direct clinical implications for our understanding of angina pectoris and acute myocardial infarction. The impossibility of measuring coronary flow in man during life and the manifold variations in the technics of postmortem studies in man and in experimental conditions in animals have led to conflicting and contradictory opinions. Differences between the architecture of the coronary tree in the dog and man have not always been appreciated.

The issue also has been confused by diverse interpretations of the term "end artery." To the anatomist an end artery is an artery which does not communicate with other arteries through any anastomotic connection so that its capillary bed receives blood from no other artery. To the physiologist an end artery is an artery which alone supplies sufficient blood to an area to maintain its function and integrity; when this vessel is occluded, the dependent area undergoes loss of function or necrosis because other arteries do not supply the given area sufficiently. These two definitions differ widely from each other; anatomic studies in other parts of the body have repeatedly demonstrated interarterial communication with vessels which physiologically are clearly end arteries.

Since Leonardo da Vinci, in one of his magnificent sketches, portrayed intercom-

munication between the coronary arteries, the interest and debate on this question have been almost continuous. Cohnheim and Schulthess-Rechberg in 1881¹ stated as a result of their studies that the coronary arteries were anatomic end arteries. It has, however, gradually become the consensus that connections exist normally between the coronary arteries, either directly or by way of fine communications of an arteriolar or capillary diameter.^{2,3} These anastomoses are readily demonstrated by the simple observation that colored watery solutions which reach the capillary bed when injected into one coronary artery promptly appear in the other coronary arteries and their ramifications.⁴

The physiologic significance of these interarterial connections, their exact nature and the circumstances which may lead to their magnification have been the subject of intensive study during the past decades. Wiggers⁵ has cogently remarked that "from a pathological standpoint it has long been accepted that the coronaries are terminal arteries, for when plugged by emboli or

¹ COHNHEIM, J. and SCHULTHESS-RECHBERG, A. Ueber die Folgen der Kranzarterienverschiessung für das Herz. *Virchows Arch. f. path. Anat.*, 85: 503, 1881.

² GROSS, L. The Blood Supply to the Heart, In Its Anatomical and Clinical Aspects. New York, 1921, Paul B. Hoeber.

³ SPALTEHOLZ, W. Die Arterien der Herzwand, Leipzig, 1924, S. Hirzel.

⁴ SCHLESINGER, M. J. An injection, plus dissection study of coronary artery occlusions and anastomoses. *Am. Heart J.*, 15: 528, 1938.

⁵ WIGGERS, C. J. The physiology of the coronary circulation. In LEVY, R. L. Diseases of the Coronary Arteries and Cardiac Pain. New York, 1936. The Macmillan Co.

thrombi in man or when artificially occluded in animals an infarct results. The rapid necrosis of cardiac tissue "could scarcely occur, were adequate anastomoses present." The failure of the supplied area to contract within one or two minutes following sudden occlusion and the electrocardiographic evidence of immediate injury are further manifestations of functional inadequacy as is indeed the common catastrophic clinical experience with patients suffering from acute coronary occlusion. Experimentally in the dog, the area peripheral to the coronary ligature becomes swollen, cyanotic and engorged and the veins appear full. Prinzmetal⁶ has recently reported that the amount of blood in such stagnant areas may be equal to two-thirds or more of the normal.

Satisfactory evidence clearly demonstrates, however, that the intercoronary anastomotic channels in the normal heart, while not preventing infarction after sudden occlusion, have some functional significance. Smith⁷ observed that following experimental occlusion of the left anterior descending artery the area of infarction was smaller than the entire territory of the distribution of this artery and its branches. Many observers have noted variation in the size of the infarct following experimental occlusion of the left anterior descending coronary artery in the dog. Indeed, in a small proportion, gross infarction does not appear at all because of the richer intercoronary connections in the dog than in man. Furthermore, following the acute occlusion of a coronary artery in the normal dog heart, cannulation of the cut artery peripheral to the tie reveals retrograde flow amounting to as much as 5.8 cc. per minute.⁸ By

⁶ PRINZMETAL, M., BERGMAN, H. C., KRUGER, H. E., SCHWARTZ, L. L., SIMKIN, B. and SOBIN, S. S. Studies on the coronary circulation. III. Collateral circulation of beating human and dog hearts with coronary occlusion. *Am. Heart J.*, 35: 689, 1948.

⁷ SMITH, FRED M. The ligation of coronary arteries with electrocardiographic study. *Arch. Int. Med.*, 22: 8, 1918.

⁸ ECKSTEIN, R. W., GREGG, D. E. and PRITCHARD, W. H. The magnitude and time of development of the collateral circulation in occluded femoral, carotid and coronary arteries. *Am. J. Physiol.*, 132: 351, 1941.

gasometric analysis this blood was found to be arterial in nature and therefore must have been derived from precapillary interarterial connections. Utilizing an injection mass which penetrates to vessels approximately 15 to 40 micra in diameter in the fixed state, corresponding to 30 to 80 micra in diameter in the fresh state, Schlesinger⁴ has demonstrated that intercoronary channels in the normal human heart are usually less than this caliber. This mass, because of its physical properties, may reach the capillary level irregularly but does not fill it or enter the coronary venous system. Only approximately 15 per cent of normal hearts reveal interarterial communications of this size and, when found, they are few in number. In contrast, 98 per cent of hearts with arteries occluded by arteriosclerotic lesions reveal collateral channels which are much more numerous, occasionally visible to the naked eye and of great functional significance. This has been demonstrated in many hearts in which, despite complete occlusions, the potentially infarcted myocardium has been free of fibrosis or other structural abnormality.⁹ Verification of this phenomenon experimentally has also been accomplished.^{8,10}

When narrowing of the coronary arteries even to occlusion proceeds gradually, first in one part of the coronary tree and then in another, complete occlusion of two or even of all three main coronary arteries may be compatible with continued life.⁹ Most patients exhibiting this condition, particularly when the third unoccluded artery is greatly narrowed, experience angina pectoris or congestive failure. Injection of such hearts demonstrates an extraordinarily rich network of anastomoses. All semblance of end arteries is lost. Available evidence indicates that two or more weeks are required for these anastomoses to become

⁹ BLUMGART, H. L., SCHLESINGER, M. J. and ZOLL, P. M. Angina pectoris, coronary failure and acute myocardial infarction. The role of coronary occlusions and collateral circulation. *J. A. M. A.*, 116: 91, 1941.

¹⁰ BLUMGART, H. L., GILLIGAN, D. R., ZOLL, P. M., FREEDBERG, A. S. and SCHLESINGER, M. J. Studies of experimentally produced intercoronary collateral circulation. *Tr. A. Am. Physicians*, 57: 152, 1942.

evident and a longer period for the development of such functionally significant connections following narrowing of the coronary arteries;⁸⁻¹⁰ vasomotor and metabolic factors as well as the differential pressure gradients between occluded and non-occluded segments of the coronary arterial tree play important rôles.

The slow development of these collateral channels emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction, contrary to the current tendency to advise earlier ambulation. Ample evidence exists that reduced cardiac work favors healing of the infarct, reduces the extent of myocardial damage, lessens liability to rupture and provides time for the development of these anastomotic channels. Similar considerations would seem to apply to patients in whom angina pectoris suddenly appears or in whom the frequency or intensity of the

attacks suddenly increases. If one can exclude temporary factors causing an increased demand for blood (fever, anemia) or physiologic reduction in coronary flow (shock, tachycardia), the sudden inadequacy of blood supply may be ascribed to structural organic narrowing or occlusion.

Such sudden imbalance of coronary circulation must always be viewed with gravity for any new reduction in coronary flow may result seriously in extensive myocardial necrosis if excessive demand is placed upon the heart before equilibrium is re-established by full development of anastomotic pathways. The slow development of a richer anastomotic circulation is also apparently responsible for the occasional clinical improvement of patients with angina pectoris, the collateral channels acting to offset the narrowing, even occlusion, which has occurred.

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A Study of Specialized Heart Tissue at Various Stages of Development of the Human Fetal Heart*

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ONE of the outstanding controversies in cardiac physiology has been that of the myogenic versus the neurogenic theory of activity. Neurogenic activity was favored in the earlier years when there was no known muscular connection between auricles and ventricles of the mammalian heart. Because nerves were known to cross the A-V groove, the impulse to the ventricle was assumed to pass over these. The heart is supplied by cholinergic (parasympathetic) and adrenergic (sympathetic) fibers, and recently it has been established that cholinergic (vagal) fibers are distributed to the S-A node, to auricular muscle, to the A-V node, to the main bundle (in some species to the proximal portions of the right and left limbs), to the coronary vessels but *not to ventricular muscle*. (Nonidez.)¹ Adrenergic fibers do not stain readily and for this reason their terminations have not been followed in detail. It is believed that they are distributed to the S-A and A-V nodes, to auricular muscle, possibly to more peripheral parts of the conducting system (Truex and Copenhaver),² to the coronary vessels (to which they are dilator) and, in addition, *to the ventricular muscle*. Most of these sympathetic trunks reach the ventricle

by crossing the A-V sulcus superficially while others accompany the A-V bundle.

His³ published the description of the A-V bundle in 1893 after which time the myogenic theory came into prominence and was almost exclusively accepted for many years because of the following reasons: (1) The bundle of His composed of non-nervous tissue had been shown to exist; (2) interruption of this pathway caused heart block; (3) interruption of other pathways did not cause heart block; (4) in the embryo cardiac pulsations precede growth of nerves into the heart; (5) the heart continues to beat when severed from the nervous system.

The myogenic theory seemed firmly established until 1940 when it was reported that although a conducting system containing Purkinje cells was present in ungulates, such a system was doubtless only vestigial in the horse and was not even present in man or in dogs. With the loss of a "bundle of His," discussion concerning the neurogenic theory was renewed. (Glomset and Glomset.)⁴

The need for reconsideration of the two theories was emphasized by description of the Wolff-Parkinson-White⁵ syndrome, a condition which is diagnosed when a

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short P-R interval is associated with a prolonged QRS in the electrocardiogram of individuals prone to attacks of paroxysmal tachycardia. Wood, Wolferth and Geckeler⁶ and Öhnell⁷ among others have reported that auriculoventricular connections apart from the bundle of His and composed of ordinary heart muscle fibers were present in the hearts of individuals who during life had presented this syndrome.

Davies and Francis,⁸ reviewed certain pertinent phases of cardiac anatomy and physiology in poikilo- and homothermic vertebrates. Although there is still diversity of opinion, they conclude that in birds and mammals muscle specialized for the initiation and conduction of the impulse (nodal and Purkinje tissue) has evolved and its distribution is described. Birds have a more extensive Purkinje system (especially in the atria) than do mammals; this is related to the far more rapid heart rates in birds. Their distinctive conclusions are:

"Collateral evidence supporting the view that nodal and Purkinje fibers are neomorphic developments in the hearts of mammals and birds is provided by their ontogeny in the mammal, minor variations in their disposition, and the occasional presence of muscular A-V connections in addition to the single A-V bundle in mammals.

"Since there is no histological specialization of the muscle fibers in any part of the heart in poikilothermic vertebrates, factors other than purely morphological must account for the different intrinsic rhythmicities possessed by the individual chambers of such hearts. A differential distribution between atria and ventricles of certain chemical substances known to be concerned in muscular contraction is described and may have a bearing on the problem."

Another valuable paper is that of Walls⁹ who studied serial sections of human embryos. The focal point of his research is stated thus:

"Accounts of the development of the conducting tissue of the human heart are few, accompanying illustrations are fewer

still, and only one writer, Sanabria,¹⁰ has described the development of the entire system. But even more than these considerations, what prompted the present study was the desire to establish, if possible, whether the nodes and bundle appear, grow and develop as do other organs of the body or whether they are simply remnants of the junctional tissues found at the S-A and A-V rings." In a description of a 10 mm. embryo he writes: "There can be no question that whereas the A-V node represents a part of the original A-V canal destined to become structurally specialized, *the bundle is a new formation which arises from that primitive nodal tissue by a process of active growth.*" (Author's italics.)

That the bundle is a new development is a view favored also by Tandler¹¹ Retzer^{12,13} Shaner¹⁴ and Davies.¹⁵ Most current texts of embryology hold to Mall's¹⁶ conclusion that the bundle is "an embryological remnant of the atrial canal of which the posterior musculature connecting the sinus and ventricle never breaks down, although showing early in development changes in structure which differentiate it from the rest of heart muscle." Truex and Copenhagen² observed numerous, delicate, pale-staining nerve fibers passing from the larger nerve bundles in close contact with Purkinje fibers but were unable to identify any perifibrillar plexuses as described by Wilson,¹⁷ Scaglia,¹⁸ Blair and Davies¹⁹ and Vitali.²⁰ They saw no "specialized terminations" on the Purkinje cells. However, they write "we could follow fine varicose fibers from their perivascular plexus to small club-shaped terminals on the surface of cardiac muscle fibers." The average diameter of heart muscle cells was found to be somewhat less than that of the Purkinje cell.

Our observations were undertaken to procure further evidence that in the human fetal heart specialized tissue either did or did not exist, was or was not accompanied by nerves, did or did not at early stages have the same appearance as ordinary heart muscle from which it later differenti-

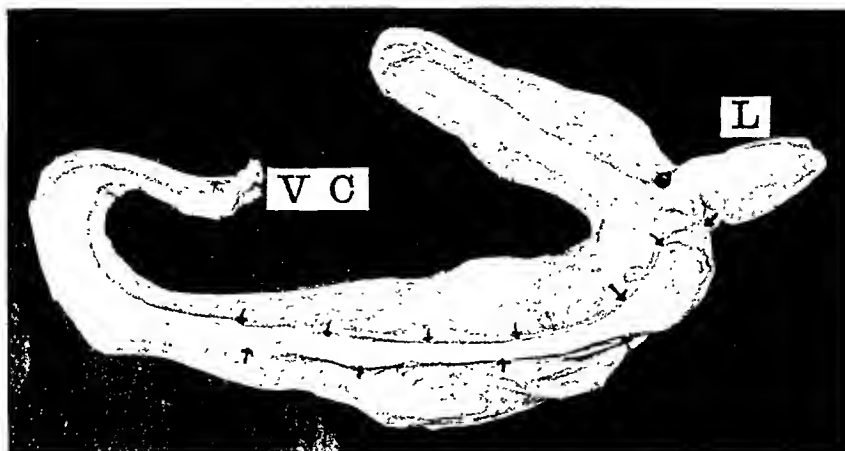


FIG. 1. Fetal heart of twenty weeks' gestation; photograph of reconstruction of S-A node. Enclosed area is orifice of superior vena cava. Projecting arm (L) indicates contact with muscles of left atrium. Arrows outline the commonly recognized "comma shaped structure, head anterior, lying in the sulcus terminalis." The smoothed surfaces are artifacts; at all surfaces numerous junctions between auricular and nodal tissue occur.

ates and finally that auriculoventricular connections apart from the bundle do or do not exist and persist.

MATERIAL AND METHODS

Four human fetal hearts were used in this investigation. They were from fetuses of fifteen and one-half, twenty, twenty-one and thirty-two weeks' gestation; the fetuses were approximately 12 cm., 16 cm., 17.5 cm. and 32 cm. c.r. length, respectively. Two of the hearts were fixed while still beating and the two others were preserved within two hours postmortem. They were injected with a fixative through all the great vessels and all the cavities to insure a rapid and adequate fixation of subendocardial structures. Each heart was then carefully dissected out and placed for varying lengths of time in the fixing solutions. Three preservatives were used: Zenker-formol, Bouin or chloral hydrate. After paraffin-rubber infiltration three hearts were cut into serial sections in the frontal plane and one in the sagittal plane. The following staining technics were used: Mallory's or Masson's trichrome for connective tissue and for general cytologic detail, Nonidez's bulk silver method for nerve staining. When the trichrome methods failed, Nonidez's technic supplied a fuller picture.

The youngest heart was sectioned at the Department of Embryology, Carnegie Institution of Washington. We are indebted to Dr. George W. Corner for the use of this specimen. The other hearts were obtained through the

courtesy of the Department of Obstetrics at the Syracuse University College of Medicine and were sectioned by one of us (C. T. K.).

OBSERVATIONS

Fifteen and One-half Week Heart. The S-A node, A-V node, main bundle and bundle branches were observed in this heart. Cells of the S-A node were found to be more widely distributed than many authors have pictured them. This node extended medially and posteriorly around the superior caval orifice in addition to the better known portion which lies in the sulcus terminalis.

With the Mallory stain, the specialized cells of the nodes, bundle and branches were larger than atrial (Fig. 2 B) or ventricular cells (Fig. 2 C); their cytoplasm took less stain and was less granular. Cross striations were not seen in specialized cells although they were readily observed in cells of the myocardium. No striking cytologic differences could be observed between cells of the various parts of the conducting system.

The A-V node was located in the lower posterior part of the interatrial septum as found by all workers. Posterior (Fig. 3 A) and anterior (Fig. 3 B) atrial connections to it were found. These pathways were vividly shown in the slides in which the

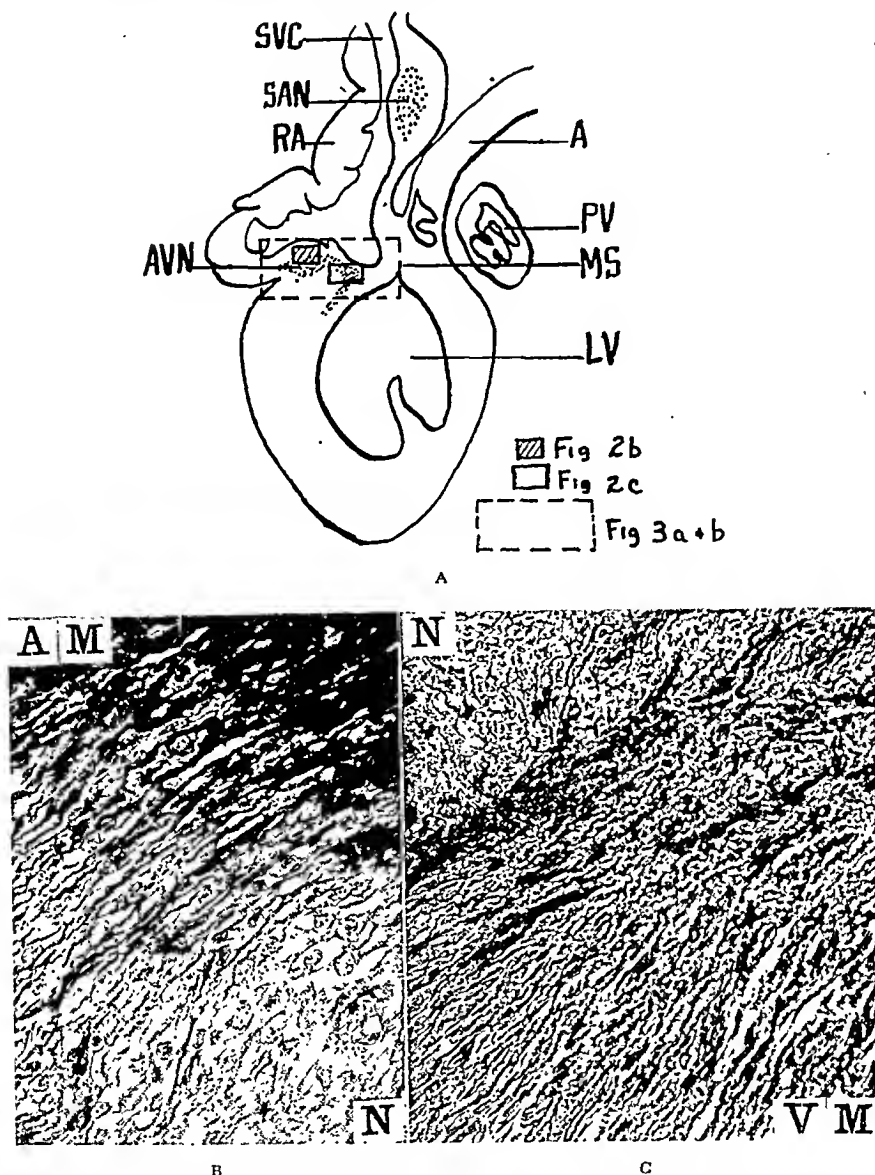


FIG. 2. Fetal heart of fifteen and one-half weeks. A, pen sketch showing orientation. Mallory stain; B, portion of sagittal section through base of interatrial septum. Above lie parallel strands of dark staining auricular muscle (AM) and below the larger, paler specialized cells of the A-V node (N). $\times 500$. C, above the large, pale nodal cells (N); strands of dark stained connective tissue produce lobulations; at lower edge is ventricular muscle (VM).

connective tissue was bright blue and the muscle cells deep red. The significance of these connections is discussed later. A sleeve of connective tissue surrounded the node but did not isolate it completely from atrial muscle. Extending from the A-V node were compact strands of cells which formed the main bundle. Right and left branches were recognized. Furthermore, on the right side of the ventricular septum more than one branch appeared. From the

main bundle and from each of the branches numerous connections to septal muscle were seen. The main bundle and branches had a much thinner connective tissue sheath than the node. No appreciable space between special cells and the connective tissue sheath could be seen.

Sagittal sections were particularly favorable for demonstrating connections of any nature between atria and ventricles. Study and reconstructions of this heart established

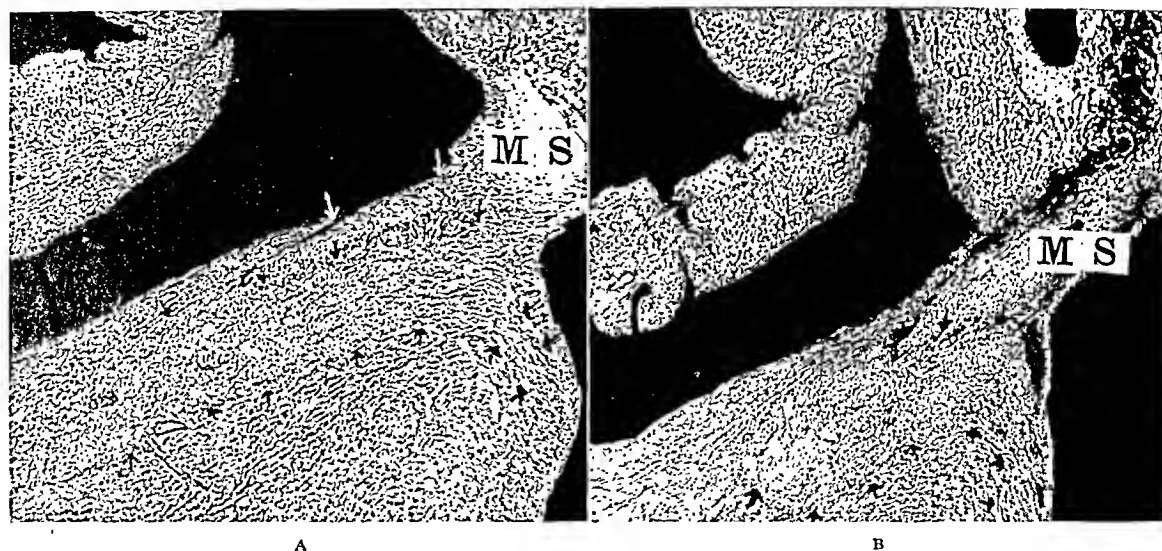


FIG. 3. Fetal heart of fifteen and one-half weeks; sagittal section. Figure 2A provides orientation. A-V node and proximal part of left branch indicated by black arrow heads; Mallory stain; $\times 55$. A, tongue-like portion of membranous septum (MS) blocks anterior pathway (between white arrows) from S-A to A-V nodes. B, here the membranous septum (MS) is narrower and an anterior pathway continuous from the A-V node via the anterior atrial wall to the S-A node is present.

that although these cells, quite different from myocardial cells, formed the A-V node and bundle of His, nevertheless they were part of a continuous muscular connection between the atrium and the ventricles. This continuity has been observed in younger hearts by other workers (Mall,¹⁶ Sanabria,¹⁰ Walls⁹).

In addition to septal atrioventricular connections other bridges between atrial and ventricular muscle were observed which were composed entirely of ordinary cardiac muscle cells. (Fig. 4.) The significance of the muscular A-V connections which occur intermittently around the A-V orifices, but especially around the tricuspid opening, will be discussed later.

Our observations on the changes in microscopic appearance of bundle branch cells as they approach myocardial cells do not enlarge upon the descriptions given by previous investigators. Bundle cells lost their more rounded contour as they merged with the more elongated ventricular cells.

In sagittal sections a large artery was cut longitudinally as it ran through the A-V nodal tissue. This corresponds to branch number nine of Spalteholz.²¹ The capillary spaces in node and bundle were less conspicuous than in the myocardium.

Twenty and Twenty-one Week Hearts. The S-A node in these hearts was identified more easily than in the younger specimen. It was found to occupy the same position described for the fifteen and one-half week heart, i.e., it formed the comma-shaped structure usually described and in addition extended medially and posteriorly around the superior caval orifice. The complete node was reconstructed in plastic, in wax and finally was cast in plaster. (Fig. 1.)

S-A nodal cells, rounder and less deeply stained than atrial muscle cells, were seen more clearly with the Masson stain. The atrial cells possessed more fibrillae and in places their cell boundaries were confluent. As was the case in the younger heart, anterior and posterior pathways, uninterrupted by connective tissue, were observed between S-A and A-V nodes which consisted of muscle and of specialized cells. However, we have not been able to reconstruct a connection consisting exclusively of specialized cells.

At this age the A-V node was a more compact structure. It had the same atrial connections as the younger heart, the more anterior of which reached the right side of the interatrial septum while the posterior connection extended to the left side of the



Fig. 4. Fetal heart of fifteen and one-half weeks; sagittal section; posterior-medial portion of tricuspid ring. A strand of atrial muscle (AM) from above passes through a funnel-shaped interruption in the darkly stained connective tissue A-V barrier to the ventricular muscle (VM); Mallory stain; $\times 350$.

septum. The cells of a part of the node were arranged in a basket-work fashion (as described by Tawara)²² which made connections to ordinary atrial muscle. In both hearts a thin slip of cells extended upward along the more anterior part of the right border of the membranous septum and became confluent with muscle of the atrial septum. Thus, four different pathways of atrial connection to the A-V node were observed: anterior to foramen ovale, from the posterior atrial wall along the base of the auricular septum and right and left connections in the septum from the more anterior part of the A-V node to the atrial musculature. (Fig. 5.)

From the A-V node cells comprising the main bundle extended downward through the membranous septum to lie on top of the ventricular septum. (Fig. 5.) In frontal section the right bundle branch (Fig. 6) was more anterior than the left and as the main bundle was followed through the septum more than one branch to the right ventricle could be seen. The left limb (Fig. 7) was the more extensive of the two.

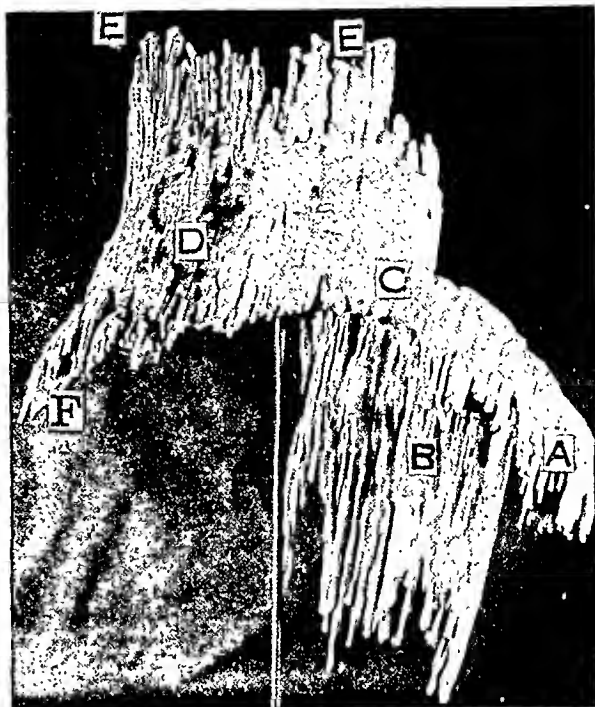


FIG. 5. Fetal heart of twenty-one weeks; sagittal view. Photograph of a reconstruction of the specialized cells which shows the more anterior right bundle branch (A), the extensive left branch (B), the main bundle (C), the A-V nodal region (D), with connections to the respective atrial walls through anterior (E) and posterior (F) pathways.

It extended broadly beneath the endocardium down the septal wall of the left ventricle. (Compare with Fig. 5.) Eventually it split into strands of cells going to the anterior papillary muscle, to the inferior papillary muscle and to the apical portions of the interventricular septum.

The main bundle gives branches directly to the septum at the more basal portion (Mahaim)²³ and indeed there are connections throughout the septum from the bundle branches.

The A-V node, bundle and branches were composed of cells recognizably different from ventricular cells. (Figs. 7 and 8.) The specialized cells contained larger amounts of clear cytoplasm, giving them a bloated appearance. Myofibrillae, although scarce and peripherally located, could be seen only in the limb cells. The only type of termination of strands of specialized cells which was seen (or for that matter has ever been described in the literature) was a gradual end-to-end transi-

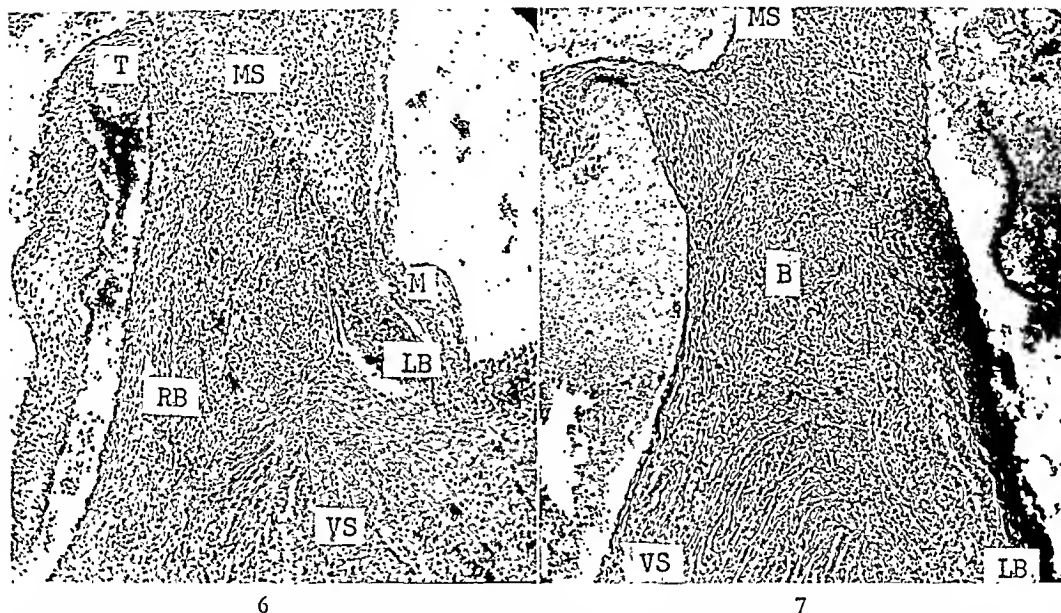


FIG. 6. Fetal heart of twenty-one weeks; frontal section through the base of the interventricular septum showing the broad stump of the right bundle branch (RB), the beginning of the left branch (LB), the ventricular septum (VS), the septum membranaceum (MS), the base of the medial tricuspid leaflet (T) and the base of the mitral valve (M) attachment to the septum. Masson stain; $\times 105$.

FIG. 7. Fetal heart of twenty weeks; frontal section at the base of the interventricular septum (VS) showing the membranous septum (MS), the main bundle (B) and the left branch (LB); silver stain; $\times 105$.

tion into ordinary muscle. (Fig. 8.) We found nothing which could be called a myoneural junction between conducting and ordinary cells. Further study of the

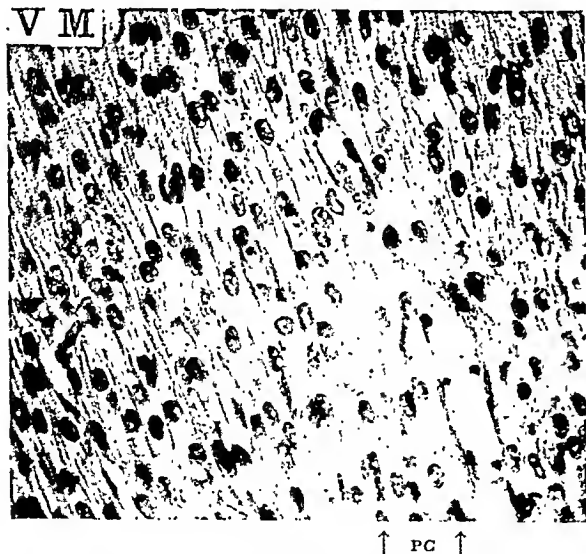


FIG. 8. Fetal heart of twenty weeks showing cytologic detail from base of a ventricular papillary muscle. At either side note parallel strands of cardiac muscle (VM); narrower diameter, deeper stained, marked cross striation. In lower center note a group of broader fibers, stained less deeply, having a few peripheral striations and a clear perinuclear space (PC). Note the transition from this band to the typical ventricular type at the top center; silver stain; $\times 500$.

areas supplied by single Purkinje strands is in progress.

The main bundle was inclosed in heavy connective tissue in these hearts. Although there was space between nodal and connective tissue, it was thought that this was the result of technic of imbedding rather than actual. Study of these two and the older hearts added nothing new to our knowledge of the blood supply of the special tissues.

This was the only heart studied for nerves to the specialized tissue and myocardium. From preliminary studies it was evident that there were a number of darkly stained fibers (presumably parasympathetic postganglionic fibers or afferent fibers) to atrial structures and to the main bundle. Since sympathetic postganglionic fibers are not differentiated with the bulk silver method, it was impossible to study their distribution. The darkly stained fibers could not be followed for any appreciable distance along the branches of the main bundle of His.

Thirty-two Week Heart. Information on the S-A node is lacking in this heart since



FIG. 9. Fetal heart of thirty-two weeks; portion of a frontal section through the base of the interventricular septum to show the A-V node (N) imbedded in the dense connective tissue of the membranous septum (MS); Masson stain; $\times 125$.

FIG. 10. Fetal heart of thirty-two weeks; frontal section through the upper part of the interventricular septum. The main bundle (B), right branch (RB), left branch (LB) and a septal branch (SB) are shown; Masson stain; $\times 125$.

the block of tissue sectioned included only those structures below the level of the foramen ovale. The A-V node and main bundle were completely imbedded in the heavy connective tissue of the upper part of the membranous septum. (Fig. 9.) Cells of the node, bundle and limbs were still, at this stage of development of the heart, larger than myocardial cells. Relatively few myofibrillae were seen in their cytoplasm.

The left limb of the bundle came off more anteriorly than the right in this heart, in contrast to the condition found in the younger ones. At this stage of development the cells of the two limbs were even more strikingly different from ordinary cells than at earlier stages; they were longer and

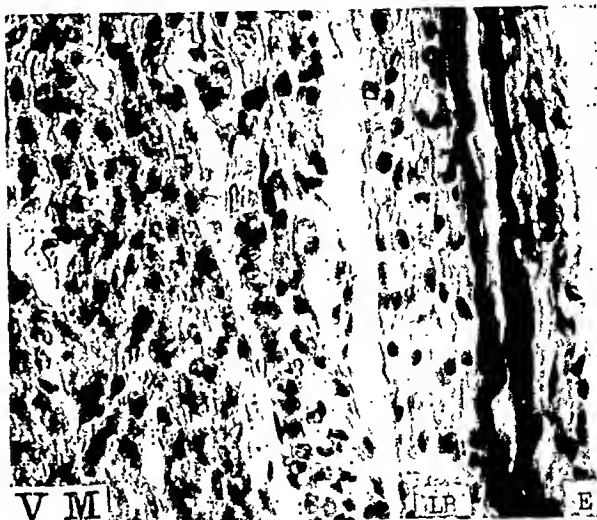


FIG. 11. Fetal heart of thirty-two weeks; portion of the left branch (LB) lying beneath the endocardium (E); to the left the heavily stained myocardium (VM). Bundle cells are more faintly striated and have a clear perinuclear space similar to a "typical Purkinje cell."

possessed more fibrillae which showed striations. There was still a clear area around the centrally located nucleus, suggestive of the Purkinje type cell. (Fig. 11.) Both limbs could be followed for greater distance in the ventricles than in the younger specimens. The right limb (Fig. 10) had assumed greater proportions at this stage. In fact, except for its length, it was nearly the size of the left limb. There were numerous septal connections from the main bundle (one of which is seen in figure 10) and from the limbs which, with the report by Mahaim,²³ establishes these connections in the human heart. They have previously been seen in the guinea pig heart (Robb and Kaylor).²⁴ As the bundle branches approached the ventricular apices more and more specialized cells changed gradually into the strictly myocardial type of cell.

This heart has not yet been examined to determine whether muscular A-V bridges are present.

SUMMARY OF FINDINGS

In three of these hearts an S-A node was found which extended around almost the entire entrance of the superior vena cava into the right auricle, that is to say, the comma-shaped structure known to lie within

the sulcus terminalis is a part but not the whole of the S-A node. (Fig. 1.) Pathways uninterrupted by connective tissue make connections from this node to the A-V node. (Fig. 2A.) One of these extends from the posterior portion of the S-A node in the sulcus terminalis, then along the posterior atrial wall, thence horizontally along the A-V junctional area to the A-V node. (Fig. 3A.) Another extends from the anterior portion of the S-A node, anterior to the foramen ovale to the upper somewhat posterior portion of the A-V node along the "raphe" of Papez²⁵ which is deep to the interatrial band. (Fig. 3B.) Still other strands from the S-A node connect through the right and left portions of the interatrial septum to the more distal portions of the A-V node and proximal portions of the bundle. None of these pathways is composed exclusively of specialized tissue. On the contrary, specialized cells appear near the nodes but then spread out to make end-to-end transitions into the ordinary atrial muscle. Not one of these pathways is near either the epicardial or endocardial surface throughout.

The silver preparations of one heart indicate that there is a considerable supply of dark stained nerve fibers to the S-A and also to the A-V node. Because there is no differential stain available for sympathetic fibers, we have no observations on their course or terminations.

From the A-V node compact bundles of specialized cells stream distally forming the bundle of His which divides into two main outflows at the top of the interventricular septum. The left outflow has been described as a broad, flat sheet which eventually separates into anterior, posterior and septal portions. This we confirm. However, we report that the right outflow does *not* consist of one single limb as commonly stated (Fig. 5) although it is usually in discrete bands and not "sheet-like" as on the left. Connections from the main bundle and from all parts of the right and left branches to septal muscle are to be seen in all of these hearts. (Fig. 10.)

In general, the cells throughout the

specialized system are alike and are different from either auricular or ventricular cells. This difference consists in the diameter being somewhat greater than that of ordinary cardiac muscle cells, the cytoplasm is clearer, there are fewer cross striations and a few peripheral myofibrillae are sometimes apparent. These cells stain less deeply with Masson, Mallory or silver technics than do ordinary muscle cells. (Figs. 6, 7 and 11.) In addition, the nodes are imbedded in connective tissue which is well differentiated with the Masson and Mallory stains. (Fig. 9.) The bundle, its branches and the Purkinje transitions into ordinary heart muscle are all enclosed in a connective tissue sheath. It is uncertain whether the small space within the sheath is an actual space during life. Our present opinion is that it may be caused by the fixing process.

We have seen nothing which could be considered to be an end organ. Whenever a Purkinje strand is followed peripherally it eventually undergoes gradual transition into an ordinary heart muscle fiber. This transition is always arranged end-to-end. A Purkinje strand never makes a right angle connection to a heart muscle cell. (Fig. 8.) We have made no new observation regarding the Purkinje-myocardial junctions nor the blood supply to this specialized tissue. We have never found an accessory bundle of His, i.e., more than one strand of specialized tissue connecting the auricle with the ventricle although we have found multiple A-V bridges of ordinary muscle.

COMMENTS

We agree with Truex and Copenhaver² whose comment regarding the moot question as to whether or not there are "typical Purkinje" cells in the human heart we commend and wish to quote:

"The existence of Purkinje fibers in various ungulates is unanimously accepted but their presence in dog and human hearts has been recently denied . . . In determining whether or not such fibers exist in man one must first decide what each author means when using the term "typical

Purkinje fiber." Is a given fiber considered typical in that it resembles the Purkinje fibers of ungulates, notwithstanding that even here it is possible for one to detect species differences? Should a fiber be called typical only if it be of large size, has a clear cytoplasmic center, has a few peripherally placed myofibrillae with less marked striation, has nuclei in groups, and possesses a connective tissue sheath? . . . When each of these attributes of a supposedly typical Purkinje fiber is found to be highly variable from fiber to fiber and from specimen to specimen, it is not surprising to find a lack of agreement in the literature. It is our opinion that the attempts to identify and specifically classify every fiber encountered by means of highly variable yet characteristic criteria, are neither justified nor necessary. In our series of human specimens we have found many Purkinje fibers which are typical in size, myofibrillar content and arrangement, etc., as shown in Figure 4. However, in the same sections we have also observed less characteristic Purkinje fibers as well as questionable fibers we could not distinguish from cardiac muscle fibers."

Blair and Davies¹⁹ preferred to use the term "Purkinje-like" to describe cells in the human bundle. We have chosen to use the indefinite appellation of "specialized" cells meaning presumably the same cells which Blair calls Purkinje-like and Truex and Copenhagen call Purkinje. Finally, in employing the term "specialized tissue" rather than "conducting tissue" we are making the term purely descriptive instead of allowing an implication of function to be included. While it is generally considered probable that these peculiar cells are the very agents which conduct the stimulus to the ventricle, nevertheless absolute proof that the sympathetic nerves which accompany the bundle and its branches have nothing to do with conduction is yet to be produced. Any cutting, crushing, ligation or injection procedure must of necessity damage these characteristic cells *and nerve fibers, too*, because of their intimate admixture.

The cells throughout the specialized system are similar, i.e., S-A, A-V and

bundle cells are more like each other than are any of these like ordinary muscle. In the oldest of these hearts the cells of the specialized tissue are more unlike myocardial cells than in the younger hearts. Indeed the specialized cells undergo a more extensive change than do the ordinary myocardial cells. On this basis we agree with Gegenbaur,²⁶ Minervini,²⁷ Nonidez¹ and with Walls⁹ that the specialized tissue in the embryo has a specific appearance and undergoes a gradual differentiation which none of the myocardial cells ever experience. Although these observations are limited and certainly do not offer any absolute proof, yet they are in accord with the opinions of Shaner¹⁴ and of Davies and Francis⁸ that the specialized tissue is an entity and not merely a persistent portion of the original cardiac tube. That truly muscular bridges connect the adult human auricle to the ventricle is also presumptive evidence that these bridges and the bundle of His have a different anlage because, although both have persisted, the cells of only the one have differentiated. The detail of changes in specialized and ordinary cardiac muscle tissue with age will need much further study.

Our observations on the S-A node differ from many others in that we find it far more extensive, offering thus more numerous contacts with auricular muscle especially deep in the septum and toward the left side. The several pathways, unobstructed by connective tissue which exist between the S-A and A-V nodes, are deeply placed in the atrial walls, a fact which makes experimental investigation difficult. Electrodes placed on either the epicardial or endocardial surface of the atrium would therefore record surface change under the electrodes but would give information neither for nor against the existence of deeper more direct pathways from one node to the other.

We find that the A-V system of specialized cells differs from the classical descriptions of Tawara,²² Monckeberg²⁸ and most modern anatomic texts which allot both septal and lateral wall supplies entirely to

recurrent branches from the apical portions of the limbs. Mahaim²³ notes direct septal connections at the base; we find them throughout the septum. Reference to Ashman and Hull²⁹ will show that this point is of some importance to the analysis of electrocardiograms. Present day interpretations are based on the assumption that no such septal connections exist.

The constancy of appearance of more than one right branch is a matter that should be more thoroughly investigated. Walls⁹ has also reported this condition. A connection along the anterior right edge of the membranous septum to one of the right branches might serve as an auriculo-ventricular conduction pathway if the main bundle were not functioning. Also if such an arrangement exists in common laboratory animals, one would need to investigate its relation to A-V block. Davies and Francis⁸ remarked in this connection: "The anomalous results obtained by Krönecker and Busch³⁰ (1899), Imehanitzky³¹ ('06) and Paukul³² ('08) in the rabbit were shown by Cohn and Trendelenburg³³ ('10) and Lloyd³⁴ ('30) to be due to the presence of early branches emerging from the bundle above the site of injury; these are not present in the dog or cat.") Since such high connections are present in human fetal hearts, re-investigation in dogs and cats would be worth while.

Either this right-sided pathway, partly muscular, partly specialized tissue, or the truly muscular bridges found could serve as accessory routes when the Wolff-Parkinson-White syndrome is present. They also might be functioning when transient, alternating right and left types of branch bundle block are present. In a previous publication (Robb and Turman)³⁵ it had been suggested that the anatomic pathway was not the only determinant of the pathway for conduction. Naturally the pathway for conduction cannot be divorced from anatomic structure but physiologic refractoriness of an existent anatomic pathway can prevent conduction. If the ordinary pathway is refractory, an appropriately timed stimu-

lus may pass over one of these accessory pathways. Thus, it is the refractory state (itself dependent on many factors) in relation to the arrival of stimuli which determines conduction pathways not mere anatomic continuity.

Kent³⁶ found muscular connections between the auricle and the ventricle on the right side, an observation which has been the source of much controversy. Wood, Wolferth and Geckeler,⁶ Öhnell⁷ and others have found such muscular connections in the hearts of individuals who had presented the Wolff-Parkinson-White⁵ syndrome. Not all the slides in our collection have been searched for such connections. In two hearts where such search has been completed, muscular bridges were found. We do not know yet and only exhaustive examination of hearts of many ages will prove whether such bridges always persist and never (or infrequently) function, or whether such muscular bridges exist only rarely and then do function. At present we only know that they are present in some embryos and that they have persisted in some hearts when during life the Wolff-Parkinson-White syndrome was known to have been present.

This paper would be incomplete if we failed to emphasize the significance of the Purkinje transitions into heart muscle. Because these terminations are "axial," i.e., end-to-end, it must follow that if this specialized tissue is the conducting system and if a wave of depolarization sweeps over this tissue onto ordinary heart muscle, the direction of such a wave *normally* must be the same as the muscle fiber direction. Hence depolarization would proceed radially from endocardium to epicardium *only where fiber direction is also radial*, e.g., where the superficial muscles penetrate at the apices and at the trabeculated area. Presumably at the ventricular bases where fiber direction varies with different layers, several depolarization waves traveling in different planes would be present.

Separate strands of Purkinje tissue are found to supply adjacent muscular areas. Such a distribution ensures rapid and pre-

sumably orderly activation of muscle always in a plane parallel to fiber direction. Since there are multiple Purkinje connections, sequential activation of muscle strands is insured although spread in muscle syncytium will be limited to the area supplied by one Purkinje strand (because adjacent areas will be almost simultaneously active and refractory). This conception agrees with data of many physiologists who have measured surface spread and found it very limited, (e.g., Harris).³⁷ We believe that only under abnormal conditions, when adjacent areas are not simultaneously refractory, does muscular syncytial spread occur. That QRS (unlike P-R) is not directly proportional to heart mass and that abnormal beats have a longer QRS than normally conducted beats also would be in accord with this theory.

The lack of a stain which will differentiate sympathetic nerves prevents observations being made which would settle the point emphasized by Truex and Copenhagen:² "any consideration of the physiological mechanism of the conduction system, which is beyond the scope of the present investigation, must take into account the fact that large bundles of nerve fibers accompany the A-V bundle and its branches." Pale-staining nerves, presumably sympathetic, accompany the bundle and its branches and other adrenergic nerves cross the A-V groove. According to Nonidez,¹ these are distributed to ventricular muscle. Complete knowledge of the exact pathways, manner of termination and function of these nerves does not exist. The present day tendency is to overlook this gap in information and concede that the specialized tissue is "the conducting pathway." Because of juxtaposition, both kinds of tissue are destroyed by experimental procedures. We must realize that the exclusive allocation of the function of conduction to the specialized cells depends on *one* type of experiment. The method was to cut or crush the bundle and allow the animals to recover. The assumption was made that if the conducting tissue were nerve, re-

generation would occur; if it were specialized cells, regeneration would not occur and the block would be permanent. The comment may be made that scar tissue barriers may prevent peripheral regeneration of axones. Such barriers are present following cutting, crushing, ligation or injection experiments at the base of the heart. Thus, we may say the presumptive (but not the absolutely proven) opinion is that the specialized tissue is the ordinary conducting pathway from auricle to ventricle. At times this pathway probably yields to one consisting of ordinary muscle fibers.

CONCLUSIONS

1. In four human fetal hearts studied, cells having characteristics similar to Purkinje cells were found.

2. One group of specialized cells, surrounded imperfectly with connective tissue, occupied the position in the sulcus terminalis conceded to be the locale of the S-A node, but, in addition, these cells extended almost completely around the orifice of the superior vena cava thus offering many more contacts to auricular muscle than the usually described node would possess.

3. A collection of these cells partially surrounded by connective tissue lies at the base of the interauricular septum just anterior to the mouth of the coronary sinus. Thus, we confirm the presence of an A-V node.

4. Several deep pathways unobstructed by connective tissue extend between the S-A and the A-V nodes. These pathways contain specialized cells and ordinary muscle cells.

5. From the A-V node somewhat parallel condensed strands of tissue pass through the membranous septum forming a structure identified as the Bundle of His.

6. The bundle ends by dividing into a broad, flat sheet of fibers on the left but in disagreement with many investigators we find more than one right branch. In addition, numerous septal connections from the main bundle and from its branches are reported.

7. Only one type of termination of this tissue is found, an end-to-end gradual transition into ordinary heart muscle.

8. Within the age space studied, there was more differentiation of specialized cells than of ordinary muscle cells.

9. The significance of these findings upon electrocardiographic interpretations, is discussed.

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Abnormal Electrocardiograms in the Absence of Demonstrable Heart Disease

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APPARENT electrocardiographic abnormalities in the absence of heart disease have been reported with increasing frequency in recent years. With few exceptions, however, the divergences have been quantitative rather than qualitative. As an example, the normal limits of the P-R interval, QRS duration and axis deviation have been considerably extended without essentially distorting the normal pattern. However, abnormalities involving the ventricular component, particularly the T wave, have generally been considered pathologic and associated with disease of the heart. We are concerned in this paper with anomalies of the T wave, particularly the T wave derived from the thoracic leads, in patients in whom heart disease could not be proven.

Almost from the first, observers have been in accord regarding the direction of T waves obtained through the use of chest leads. However, because of the different technics employed these were variously described as normally inverted (earlier methods) and as normally erect (present technic). For example, Shipley and Halloran¹⁶ published their observations on 200 normal men and women between the ages of twenty and thirty-five and noted inverted T₄ (old technic) in all. More recently Skulasen and Larsen¹⁷ made a comparable study in the thirty to fifty year age group and found upright T waves in the chest leads (present methods, normal as taken).

In a group of 299 college students Wood, Wolferth and Miller²² found three diphasic and one inverted T₄, the last in a young

man with valvular heart disease. All the rest were erect.

More recently Graybiel et al.³ made five lead electrocardiograms (limb leads, *ivf* and *ivr*) on 1,000 healthy young aviators and noted two diphasic T waves in *ivf* and none in *ivr*. No frankly inverted T waves were seen.

In a large study Edeiken, Wolferth and Wood² reported twenty-six instances of T₄ abnormality in adults demonstrating normal limb leads. However, all had some type of organic heart disease. The authors concluded that changes in the precordial leads should not be disregarded but should stimulate further search for evidence of heart disease. In their experience an upright T₄ (abnormal as taken) in an adult was never seen where "there was no significant disease of the heart."

However, apparently normal precordial T wave variants have been reported in the literature and in texts. Katz⁷ states that the T wave in *cf*₂ is sometimes normally inverted in adolescents and rarely in young adults. Sodeman¹⁸ described an abnormal T wave from the chest leads of a normal, healthy, twenty-four year old nurse without any evidence of heart disease.

Shanno¹⁵ who made electrocardiographic studies in one hundred student nurses between the ages of eighteen and twenty-two found negative T waves six times in *cf*₂, once in *cf*₃ and not at all in *cf*₄. Neither Shanno nor Sodeman offered any explanation for these aberrations.

In 1943 Dupuy¹ published several grossly abnormal electrocardiograms from apparently healthy soldiers who did, however,

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have cardiovascular complaints which were considered to be functional. The T wave abnormalities appeared in all leads and could be reversed by rest and sedation.

Also in 1943 Thompson¹⁹ described similar changes in certain susceptible individuals during hyperventilation. T wave abnormalities were seen in all leads in subjects with anxiety neuroses manifested by tachycardia, precordial pain and hyperventilation. The author expressed some uncertainty as to whether such individuals had perfectly normal hearts and considered the possibility that alkalosis resulting from hyperventilation caused further constriction of coronary vessels already altered to a subclinical degree.

In a recent communication based on electrocardiographic findings from 300 negro and 200 white normal adults, abnormal precordial T waves were noted in 4.6 per cent of the negroes and .5 per cent of the whites (one case).¹¹ Careful studies indicated that none of these people had organic disease of the heart. The aberrations were observed more frequently in negro women than in men, in individuals who had normal-sized or small hearts and who had a tendency to right axis deviation.

It was concluded that this represented a persistence of the juvenile form and was not a manifestation of organic heart disease. In support of this was the observation that the limb leads were all normal, that when the right arm was used as the indifferent electrode the T waves were commonly erect and finally that the precordial T waves tended to alter their direction with the passage of time.

Unfortunately, clinical studies on the direction of the T wave are of necessity on an empirical basis. Although it is truthfully stated that the T wave is coincident with restitution in the ventricles and the retreat of electrical activity, this merely constitutes a statement of fact and does not establish a causal relationship. In his textbook on electrocardiography Katz⁷ suggests that the direction of the T wave is determined by the fact that the geometric pattern

of restitution differs from the pattern during activation and prevents the electrical field during retreat from being opposite to that field during excitation. This is in agreement with observations that the base of the ventricles lags behind the apex during restitution and the right ventricle lags behind the left.

One of the most illuminating studies to date is that of Hoff, Nahum and Kisch⁵ who were able to dissociate the ventricles by the use of potassium salts applied locally to the heart. They thus obtained pure dextro- and levo-cardiograms. These tracings were quite different from those derived from the intact, untreated heart and showed no trace of a T wave. However, the algebraic sum of the graphs derived separately from the left and right ventricles reconstituted the original normal tracing complete with T waves.

They concluded that the T wave resulted from interference of the terminal portions of the dextro- and levo-cardiograms. An upright T wave occurred when the dextro-cardiogram was of greater duration than the levo-cardiogram, and an inverted T wave occurred when the opposite was true. By chilling the left ventricle and causing prolongation of the ventricular complex on the left side, a negative T wave was obtained.⁴ Similar changes followed heating of the right ventricle. When the right ventricle was chilled or the left heated, the T wave became higher.

These observations are valid for limb leads and probably also for precordial electrocardiograms. In support of this experimental demonstration are the T wave changes resulting from chilling of the heart after the ingestion of ice water.²¹

Although the work of Nahum, Hoff and Kisch doubtless explains the T wave inversion noted in disease and injuries of the heart, it does not provide the answer to the inverted precordial T waves found in many children and some adults, particularly in those in whom the limb leads are normal. Earlier work by Katz and his associates^{8,9,10} indicated that the nature and conductivity of the tissues immediately adjacent to the



FIG. 1. Case I. A, obtained on admission; B and C, lead IVF, recorded three days later.

heart had a profound effect on the character of the electrocardiogram. Robinow, Katz and Bohning¹³ who considered the problem of T_4 in children concluded that differences in the shape of the chest in juveniles as compared to adults accounted for much if not all of the character and direction of T_4 in children.

The cases to be described in this paper are intended to illustrate a group of anomalies largely concerned with precordial T waves in individuals without demonstrable heart disease. They were found over a period of approximately eighteen months during which time some 5,000 electrocardiograms were read. The high incidence is doubtless fortuitous since a much greater number of tracings had been observed earlier without a comparable number of similar anomalies. With one exception these individuals had no complaints referable to the heart. In that case the symptoms were considered to be due to a marked cardiac neurosis and aerophagia.

CASE REPORTS

CASE I. A twenty-nine year old white soldier was sent into the hospital from the separation center because of frequent extrasystoles. The patient was not aware of the arrhythmia and had no complaints referable to

the heart. His previous health had always been good and the past history was non-contributory.

Physical examination revealed a well developed and nourished white man who was moderately nervous. The heart was not enlarged; the rate was 90 and numerous extrasystoles were noted. These were diminished but not abolished by exercise. A soft systolic murmur was heard in the beats succeeding the extrasystoles. The blood pressure was 120/70; temperature was normal; the sedimentation rate was 3 mm. per hour; the white blood count was 7,400; the urinalysis was normal and the Kahn test was negative. The basal metabolic rate was -4 . The chest and heart were normal to radiography and fluoroscopy. Exercise tolerance was good.

The electrocardiogram revealed the presence of alternating ventricular premature beats. There was no important axis deviation and the ventricular components of the sinus beats in the limb leads were normal. In lead IVF the T waves of the sinus beats were sharply inverted. After several days during which no medication was given the patient became less nervous and fewer extrasystoles were noted. An electrocardiogram made at this time demonstrated T wave inversion only in the beats which followed the extrasystoles. Where a number of normal beats occurred in succession the first T wave was inverted, while those which followed were erect and quite within normal limits. With recurrence of the bigeminal rhythm the tracing resembled that made on admission. (Fig. 1.)

Comment. This soldier had no cardiac complaints, and unless extrasystoles are considered to be evidence of heart disease none could be demonstrated. To be sure, the T_4 abnormalities noted on the first tracing were alternating in character. However, where the only other beats present were ectopic in nature, the only conclusion which could be drawn was that T_4 was abnormal and possibly pathologic. Subsequently, when the extrasystoles became fewer in number, it became obvious that the anomaly occurred only following premature beats and was in some manner associated with them.

Recently Scherf¹⁴ reported lowered and inverted T waves in various leads following extrasystoles. He considered that this probably indicated the presence of heart disease, particularly since it was noted only three times in the absence of cardiac illness. The mechanism was believed to be connected chiefly with changes in the filling of the heart.

In Case I alterations in cardiac filling were doubtless extensive. Considerable overdistention must have been present during the pause following the ectopic beats to account for the systolic murmur heard with each succeeding beat. How this was responsible for the T_4 inversion is not, however, plain. Any change in the coronary circulation could hardly have manifested itself so promptly or disappeared so soon.

CASE II. A twenty-six year old white officer was seen in consultation because of a cardiac murmur which was said to have been heard from time to time. Otherwise the history was entirely unremarkable. There were no cardiac or other complaints of any sort.

He was a tall, slim young man who appeared neither acutely nor chronically ill. Except for a moderate funnel deformity of the chest the examination revealed nothing abnormal. The heart was not enlarged, the rate was moderate and the rhythm was regular. The first sound at the apex was impure and the second sound was occasionally reduplicated. No murmurs were heard and no thrills were felt. The blood pressure was 122/78.

Urinalysis was negative, the white blood

count was 5,900, hemoglobin 90 per cent, sedimentation rate 2 mm. per hour and the serology was negative. The temperature was normal. X-ray of the chest showed the heart to be of normal contour with a transverse diameter of 12.8 cm., exactly average according to the tables of Ungerleider and Gubner.²⁰ All of the cardiac function studies were within normal limits.

The electrocardiogram showed a sharply inverted T wave in CF_2 , a lesser inversion in CF_3 and an erect wave in CF_4 . The CR leads all had erect T waves. Repeated tracings over a period of one month remained unaltered.

CASE III. This twenty-three year old negro soldier was one of a group of normal young people selected as subjects for an electrocardiographic survey. He had no complaints of any sort, used no drugs and had never been seriously ill.

He was 69 inches tall and weighed 140 pounds. The heart was entirely normal to physical examination and his exercise tolerance was excellent. Blood pressure was 120/82. According to the Ungerleider and Gubner tables²⁰ his heart size by radiography was 9 per cent below average normal. Hemoglobin was 104 per cent, the white blood count 7,600 and the erythrocyte sedimentation rate was 4 mm. per hour.

The electrocardiogram showed essentially normal limb leads and axis deviation. The T waves in $CF_{2,3,4,5}$ and 6 (5 and 6 not shown) demonstrated varying degrees of inversion. The TCR waves, however, were erect and normal. Two other tracings made over a one-month period was unchanged.

Comment on Cases II and III. These two cases were considered to represent persistence of the juvenile pattern in the electrocardiogram of adults. (Fig. 2.) The study of negroes and whites noted earlier¹¹ indicated that a significant number of negroes retained the juvenile configuration of the chest leads into maturity. The incidence of this phenomenon was very much smaller in whites but it did occur. Careful study of these individuals indicated that this constituted a normal variant and was not the result of myocardial disease.

Katz⁷ in his textbook on electrocardiography states that the T wave in CF_2 is

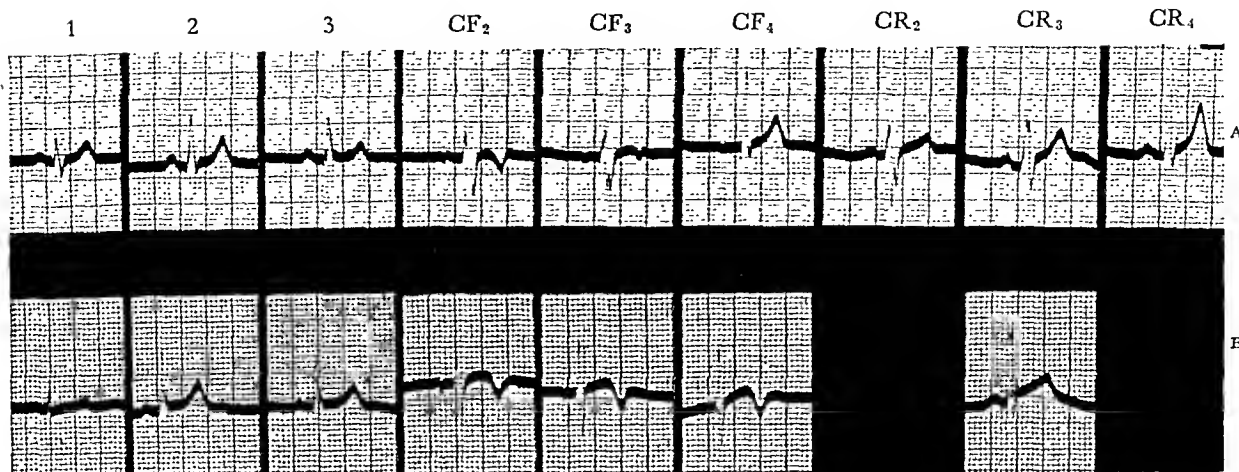


FIG. 2. Examples of juvenile electrocardiograms in adults; A, Case II; B, Case III.

occasionally diphasic or inverted in normal young adults. In Case II this inversion was present also in CF_3 while in Case III it persisted all the way to CF_6 .

The electrocardiographic pattern of youth is rather characteristic and not easily confused with other similar deviants.¹² The limb leads are ordinarily entirely normal but may show slight degrees of right axis deviation. The T waves may be diphasic or inverted from CF_2 all the way through CF_6 but are generally inverted only in the leads nearest the sternum, CF_2 , CF_3 and occasionally CF_4 . T wave inversion is never seen in CF_4 or CF_5 without equivalent or greater inversion in CF_2 and CF_3 . TCR_2 is very rarely diphasic or inverted but is usually erect. The T wave was not observed to be inverted in the other CR positions.

T wave inversion in chest leads of children is thought to be the result of a tendency to right axis deviation and to a difference in the configuration of the puerile chest as compared to that of the adult.¹³ However, such a difference could not be demonstrated in these cases.

CASE IV. This twenty-six year old white soldier was one of a group of normal individuals on whom an electrocardiographic survey was made. He had no cardiac complaints of any sort and had never been seriously ill. He was a well developed and somewhat obese young man and the physical examination was entirely normal. The heart was not enlarged to percussion, the rate was moderate and the rhythm

was regular. No murmurs were heard and no thrills were felt. The blood pressure was 128/84. Exercise tolerance was excellent.

The urinalysis, blood counts, hemoglobin, erythrocyte sedimentation rate and serology were all normal. X-ray of the chest demonstrated a heart which was somewhat transversely placed but which was not enlarged or distorted. The lungs were normal.

The first electrocardiogram obtained demonstrated left axis deviation, low amplitude of T waves generally, questionably diphasic T_2 and inverted T_3 . The T in CF_2 was small and multiphasic; it was slightly but definitely inverted in CF_3 and CF_4 and in CR_2 , CR_3 and CR_4 .

One month later there was no significant change in the limb leads but the T wave inversion in the chest leads had become exaggerated and involved CF_2 which previously had been mostly upright. The greatest inversion was noted in CF_3 and in CR_3 .

After a lapse of one more month an electrocardiogram demonstrated significant increase in the height of T_2 while T_3 was more deeply inverted. All of the waves from the thoracic leads had become erect although they still were somewhat low. (Fig. 3.)

Throughout this period of observation there were no complaints referable to the heart and no evidence of infection or inflammation.

CASE V. A twenty-two year old white soldier who had completed three years of service was sent into the hospital because of cardiac arrhythmia and a murmur. He had no complaints of any sort. Until the age of nine he was said to have had some sort of fever each summer (possibly malaria) but never had scarlet fever or rheumatic fever. At the age of six he was

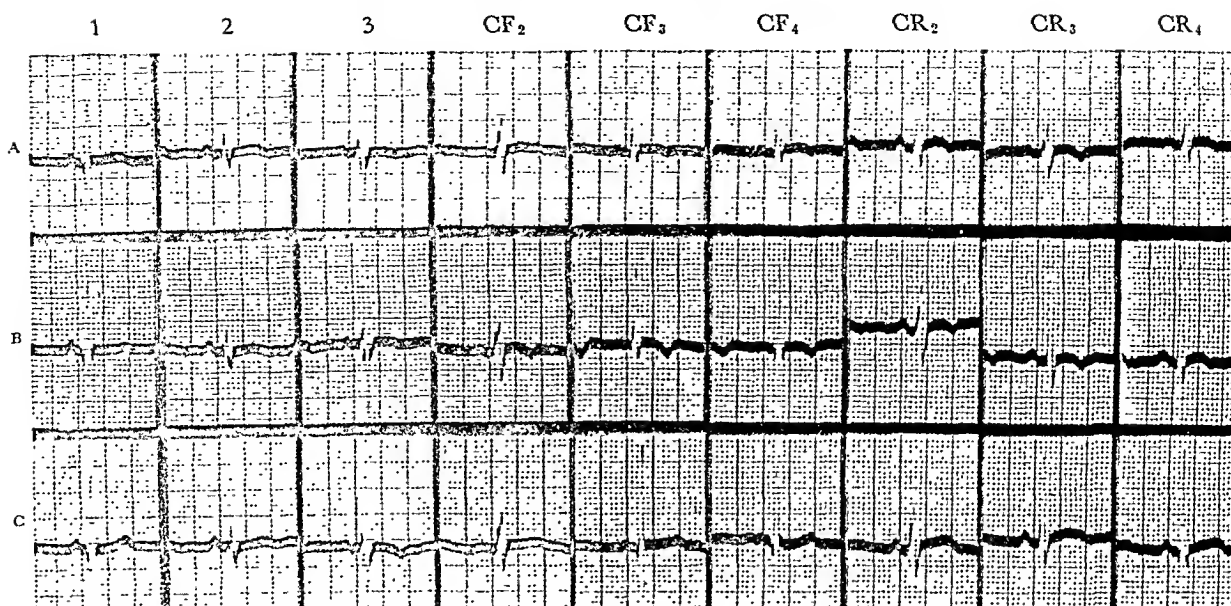


FIG. 3. Case IV. A, first electrocardiogram; B, obtained one month later; C, obtained two months later.

injured in a dynamite blast which destroyed the sight of the right eye. Shortly before coming into the army he had an appendectomy.

Physical examination revealed a well developed and nourished young man who did not appear ill. There was a large corneal opacity of the right eye. The heart was not enlarged to percussion. The rate was 76 and there was a marked sinus arrhythmia. A very soft systolic murmur was localized over the apex. No other murmurs were heard and no thrills were felt. The blood pressure was 128/76. All of the reflexes were normal and the examination was otherwise entirely unremarkable. Exercise tolerance was excellent.

The urine was normal, serology negative, white blood count 8,200 and the sedimentation rate was 8 mm. per hour. X-ray of the chest revealed a heart which was neither enlarged nor distorted. Fluoroscopy added no further information.

An electrocardiogram made shortly after admission to the hospital showed marked sinus arrhythmia. The axis was vertical and T_1 was somewhat low. The T wave in CF_2 was upright, it was inverted in CF_3 and CF_4 , upright in CR_2 and diphasic in CR_3 and CR_4 . Three days later there was no significant change in the limb leads nor were changes seen in these leads at any time subsequently. TCF_3 , however, had become diphasic and TCF_4 was inverted to a lesser degree than formerly. TCR_3 had become more negative than before.

Approximately one week after his admission

to the hospital a complete tracing demonstrated upright and adequate T waves in all of the CF and CR leads. A few days later inversions were again apparent and this time negative elements were present in the T waves of CR_2 and CR_3 which had previously been entirely upright. The last tracing taken several days later showed only a diphasic TCF_3 and TCF_4 . (Fig. 4.)

Occasionally varying degrees of T wave inversion could be seen in successive beats of the same tracing. When this happened, the greatest degree of T wave inversion was seen in the beats which followed the longest pauses during the course of the sinus arrhythmia.

During the period of observation this patient had no complaints nor did he manifest any evidence of infection or inflammation. The temperature was continuously flat and the white blood count and sedimentation rate did not vary significantly from those obtained on admission.

CASE VI. An eighteen year old white soldier was seen at the cardiac clinic at the request of his commanding officer for the purpose of determining whether he should be retained in a limited service capacity because of heart disease. As a child he is said to have had a murmur which was observed over a period of years by his family physician. Directly after coming into the army he was hospitalized because of his history and later placed on a limited service status. The patient knew that he had "heart disease" but was exceedingly vague as to symptoms. Although there were no complaints

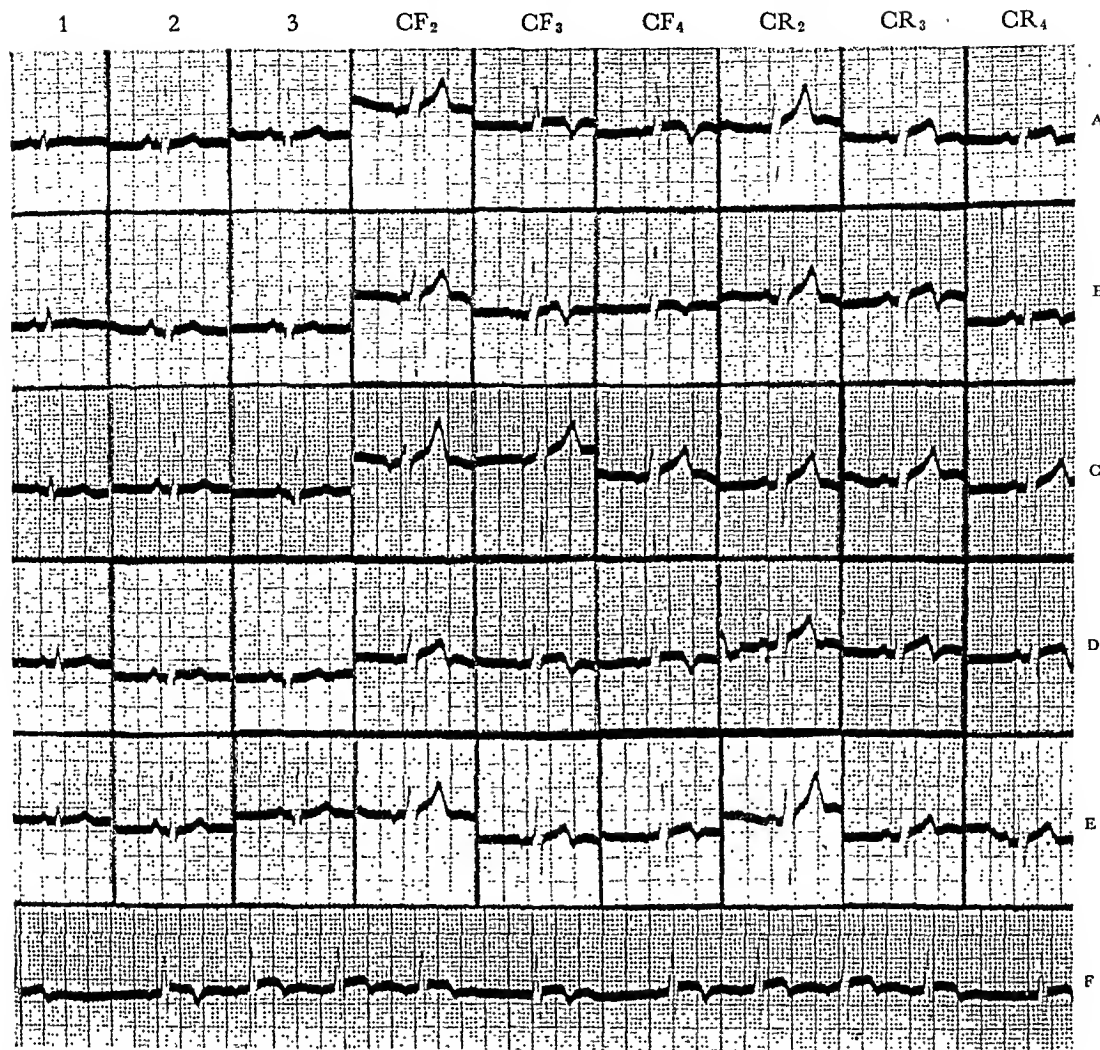


FIG. 4. Case v. A, obtained on admission; B, recorded three days later; C, recorded seven days later; D, recorded ten days later; E, recorded fourteen days later; F, lead CF_3 made at same time as D above.

directly referable to the heart, he had an active cardiac awareness and neurosis.

Physical examination revealed a well developed and nourished young man who did not appear acutely or chronically ill. The head and neck were normal and there were no abnormal cervical pulsations. The chest was symmetrical and the lungs were clear. The heart was not enlarged, the rate was 70 per minute and the rhythm was regular. The sounds were good and no murmurs or thrills were noted. The blood pressure was 110/68. The abdomen, extremities and reflexes were all normal. Exercise tolerance was excellent.

The urine was normal, the serology negative and blood counts, hemoglobin and sedimentation rates were all well within normal limits. The temperature was flat at all times and there was no evidence of infection or inflammation.

A complete electrocardiogram was made shortly after admission which showed sinoauricular rhythm and a normal axis. T_1 was inverted and T_2 was very small and multiphasic. T_{CF_2} was normal; T_{CF_3} was diphasic and T_{CF_4} and T_5 were inverted. Similar changes were seen in the T waves of the CR and CL leads.

Repeated tracings over a period of time showed no significant changes from the one made originally. However, following very vigorous exercise a curve could be regularly obtained which was quite within normal limits. (Fig. 5.) T_1 and T_2 would then appear upright and were of normal amplitude. Leads CF_4 and CF_5 which generally showed the greatest degree of T wave inversion acquired T waves which although somewhat low were upright and essentially normal.

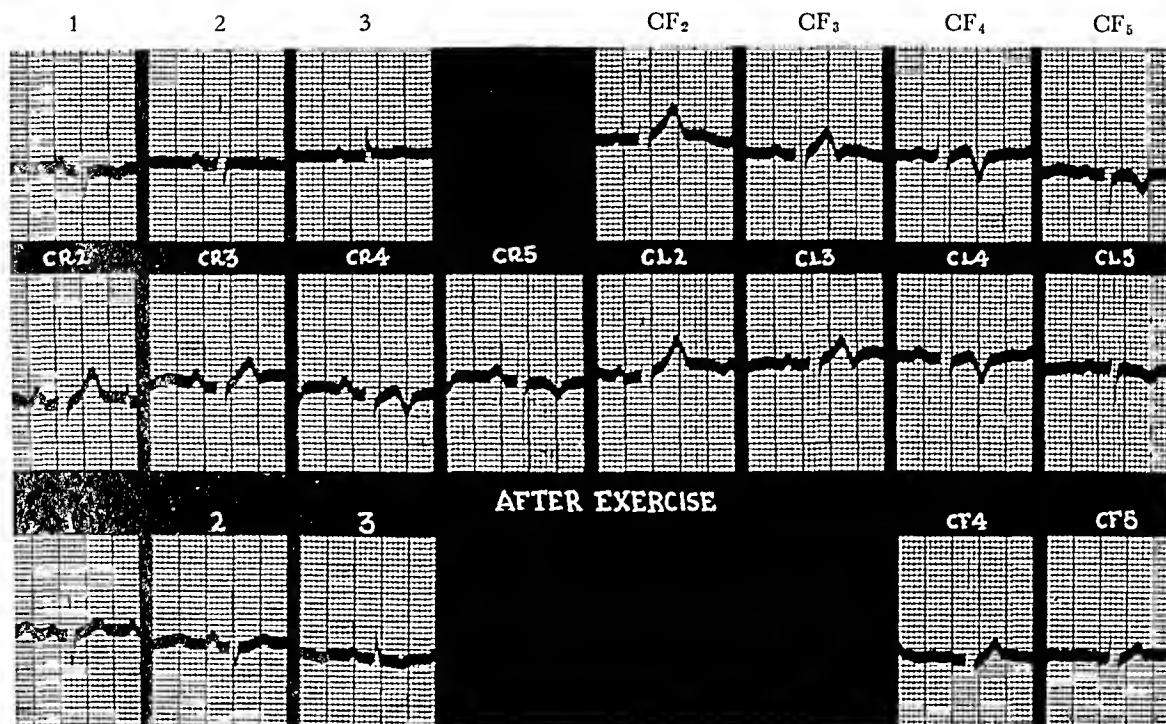


FIG. 5. Case IV. Upper tracing as indicated obtained on admission; lower tracing record following vigorous exercise.

CASE VII. A twenty-two year old white man was admitted to the hospital with a diagnosis of chronic pericarditis. He had no complaints. Two years earlier while in the armed forces he awoke one morning with an indistinct, dull pain in the chest which was made worse by deep breathing. He was subsequently hospitalized and studied for ten weeks. The pain persisted for approximately ten days but was unassociated with fever, chills, cough or feeling of illness. Eventually he received a medical discharge for what is said to have been chronic pericarditis. The earlier history was non-contributory.

Upon his return to civilian life he did nothing for some months. Later he was examined at a Veterans Hospital and advised to return to work as no evidence of disease was present. He did this but after two weeks he became aware of retrosternal discomfort and was admitted to another Veterans Hospital for study.

Physical examination revealed a well developed and nourished young man who did not appear ill. The heart was not enlarged, the rate was moderate and the rhythm was regular. The sounds were excellent and no murmurs or other adventitious sounds were heard. The blood pressure was 110/80. There was no increase of the venous pressure, no edema and no ascites. The lungs were clear and no abdominal organs

were felt. The white blood count was 6,300 and the sedimentation rate was 5 mm. per hour. All other laboratory studies were entirely within normal limits. Throughout the period of observation the temperature was normal and there were no complaints or indications of active disease of any character.

X-ray of the chest revealed normal lung fields and a heart which was normally placed and neither enlarged nor distorted. Fluoroscopy revealed no evidence of individual chamber enlargement and the cardiac pulsation was ample and unhibited.

The electrocardiogram on admission was grossly abnormal. T wave inversion was apparent in L_1 , L_{II} , CF_2 , CF_3 , CF_4 and in CR_2 , CR_3 and CR_4 . The QRS complex, however, was not remarkable and there were no significant deviations of the S-T segments.

Subsequently tracings were made under various conditions in an effort to determine the validity and constancy of the findings. They were obtained before and after exercise, the administration of atropine and of prostigmine, breathing of 100 per cent and of 10 per cent oxygen, on an empty stomach, a full stomach and in various positions. Regardless of the conditions imposed the electrocardiogram remained unchanged and abnormal until a con-

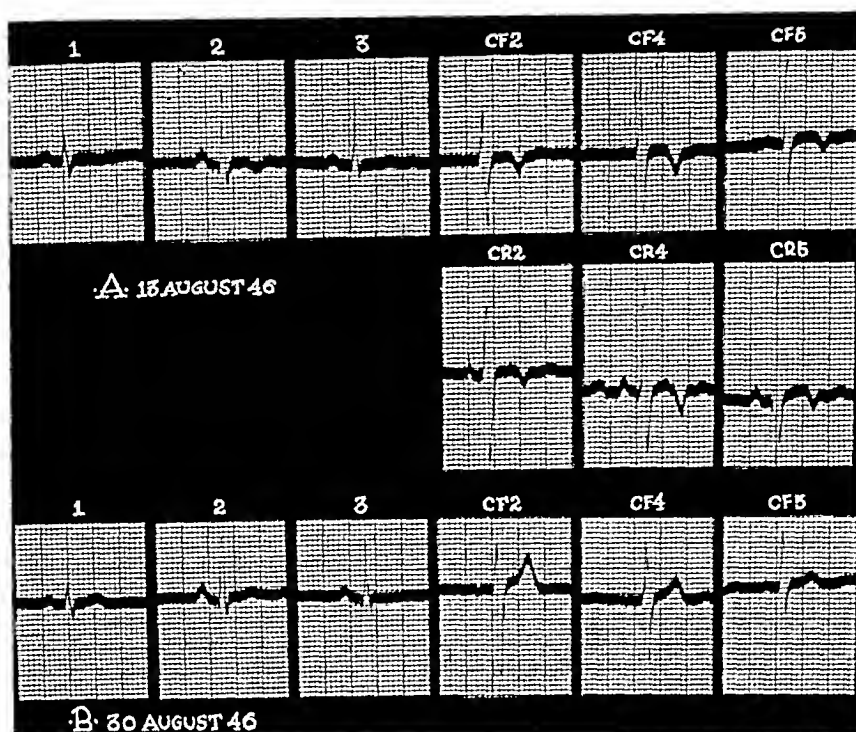


FIG. 6. Case VII. A, obtained on admission; B, spontaneous reversion to normal.

trol tracing was made prior to the administration of 100 per cent oxygen. This occurred some two weeks after his admission to the hospital. This curve showed diphasic-to-upright T waves in the limb leads and in CF_4 while TCF_2 was frankly upright. No additional changes occurred after breathing 100 per cent oxygen. Two days later the tracing became entirely normal and has remained so. (Fig. 6.) It must be emphasized that during the period of observation there was no change in the laboratory findings or in subjective sensations.

Eventually the patient was released after being told that there was no evidence of heart disease and advised to return to work. He was instructed to return at stated intervals for additional examinations.

Comment on Cases IV, V, VI and VII. These cases are grouped together because of their several common features. The limb leads contained T wave deviations which varied from lowering and flattening to frank inversion. The most spectacular abnormalities, however, were noted in the thoracic leads. The greatest degree of inversion of the T wave occurred at or near the apical position. In this respect they differed from Cases II and III in which the points of greatest T wave negativity were

at or near the sternal border and then only in the CF leads. The QRS complex and S-T segments were normal. In all these subjects essentially normal curves were obtained with the passage of time or following vigorous exercise.

The possibility of obscure but real myocardial disease in these individuals cannot be overlooked. Although the first patient was never aware of any illness, the second had a series of conditions any of which might have resulted in organic changes in the heart. The third is said to have had a murmur in childhood while the last patient must certainly have had something abnormal to result in ten weeks' confinement in an army hospital. The record is not clear on this point, however, and the abnormality may well have been confined to the electrocardiographic findings.

In spite of the possibility that organic changes might be present in these individuals, no diagnostic means at present available served to substantiate this claim. It will be recalled that in none of the patients at present under discussion was there any alteration in laboratory or x-ray findings nor were there any unusual physical

findings. We have here the curious phenomenon of abnormal electrocardiograms which righted themselves following the passage of time (days to weeks) or after vigorous exercise in the absence of any evidence of disease activity.

If we can discount the possibility of associated organic changes, and this seems reasonable, the mechanism of the unstable T wave, although obscure, becomes susceptible of analysis. Hoff, Nahum and Kisch⁵ who made experimental studies of the T wave concluded that the direction of this portion of the electrocardiogram was dependent upon slight but constant asynchrony of the terminal electrical phenomena of the ventricles. Organic or functional delay in that portion of the electrocardiogram derived from the left ventricle led to inversion of the T wave; the same change also resulted from shortening of the right side. One may be forgiven perhaps for postulating that some normal hearts do not possess the same degree of ventricular asynchronism but instead exhibit an unstable equilibrium manifested by varying direction of the T wave. This could be the result from minute changes in synchronism such as might in other normal hearts merely cause slight lowering or heightening of the T wave. Another possibility to be considered is that some normal individuals are possessed of an unusually labile or exaggerated asynchronism of the terminal portion of the ventricular complex leading to the same result. For example, the T wave inversion obtained by means of ice water ingestion occurs much more promptly in some subjects than in others and cannot be performed at all in some individuals.

It is suggested that these patients represent instances of normal hearts with normally unstable T waves.

CASE VIII. A twenty-three year old white soldier who had completed four years of army service was sent into the hospital from the separation center because of a complaint of shortness of breath and rapid beating of the heart. At the age of seven he had pneumonia and this occurred again when he was fourteen.

When he was eighteen years old he is said to have had mumps which was then followed by some type of heart condition. He was given digitalis for this and took the drug until his enlistment in the army when he stopped the medication. He went through several campaigns and served vigorously and without difficulty until approximately three months before his discharge. At this time he became aware of precordial discomfort, shortness of breath and rapid heart action. During the same interval he lost approximately 15 pounds.

Examination revealed a very well developed and nourished young man who exhibited sighing respiration but who otherwise did not appear ill. His head and neck were normal. The chest was symmetrical and the lungs clear. The heart was not enlarged, the rate was moderate and the rhythm regular. The sounds were of good quality and no murmurs or thrills were noted.

Several urinalyses showed good concentration and were free of albumen and sugar. The hemoglobin was 104 per cent, the white blood count 8,450 and the sedimentation rate 4 mm. per hour. The basal metabolism was -7 and the serology was negative. X-ray of the chest demonstrated normal lung fields and a heart which was not enlarged. Fluoroscopy added no further information. A gastric analysis was normal and a gastrointestinal series was negative except for the demonstration of a cascade stomach and a high splenic flexure. All cardiac function studies were normal.

The first electrocardiogram made shortly after admission demonstrated normal limb leads with sinus rhythm and normal axis. T wave inversion was apparent in CF_2 , CF_3 , CF_4 , CR_2 and in CR_3 . One morning several days after admission the patient was sedated with 3 gr. of seconal and an electrocardiogram made while he was asleep. This curve was entirely normal in all leads. Accordingly, an attempt was made to duplicate this result by the use of hypnosis. This was done the following afternoon but the tracing obtained was abnormal and identical in appearance to that made on admission. At this time a dose of seconal was administered and when this had become effective another tracing was made. However, this one also was abnormal.

The following day a complete electrocardiogram was made before the patient got out of bed. He was then sedated and another curve obtained. At this time it was noted that the tracings made before sedation and after sedation

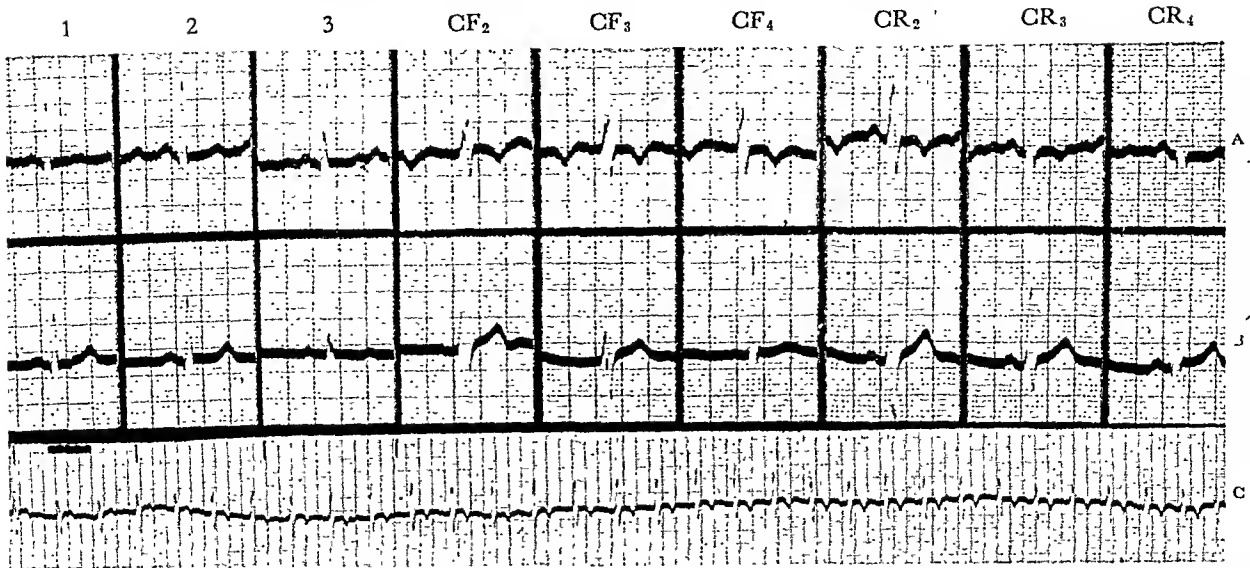


FIG. 7. Case VIII. A, obtained on admission and thereafter in the afternoon; B, obtained before eating in the morning; C, continuous IVF tracing obtained before and during inflation of the stomach. Injection of air began with the second beat.

were both normal. It later became apparent that the curves obtained in the morning before the patient had eaten were normal while those made later in the day appeared abnormal and pathologic. No significant changes were observed following exercise, hyperventilation or the administration of atropine or prostigmine.

On several occasions the stomach was completely evacuated in the morning and then distended with air. A continuous curve made during this procedure demonstrated first depression then inversion of the T wave while the stomach was inflated. Before the air was injected and after it was removed the curve was normal. (Fig. 7.)

Comment. It is entirely possible that this patient had some degree of myocarditis following his attack of mumps four years earlier. However, it is doubtful if this could have produced changes later manifested by changes in the electrocardiogram during distention of the stomach. There was no evidence of heart disease by physical examination, x-ray or any other diagnostic procedure. The sighing respiration was believed to be due to a very active cardiac neurosis and was not present when the patient was reading or occupied with other diversions. Much of the gastric distention was thought to be the result of air swallowing.

It appears likely that the electrocardiographic anomalies in this case were in some

manner associated with the state of filling of the stomach and possibly the colon. The exact modus operandi, however, is obscure. It is doubtful if the physical presence of air or food in the stomach could result in the changes noted. On the other hand, such effects could conceivably result through retrograde stimulation of the vagus or sympathetic systems. However, the administration of atropine and of prostigmine produced no significant alteration of the curve.

CASE IX. An eighteen year old white soldier was sent to the hospital with a diagnosis of coronary thrombosis and a complaint of severe substernal pain which radiated to the neck and shoulders. This occurred some two hours earlier without physical strain while he was seated at a desk. He felt somewhat more comfortable in the erect position than when recumbent. The past history was entirely non-contributory.

The patient was pale and sweating when first seen and in slight shock. The temperature was 97.8°F., the pulse 96 per minute and the blood pressure 120/76. Due to his condition the examination was carried out in the supine position. The lungs were apparently normal and the heart was remarkable only in that percussion was unsatisfactory and the sounds were distant.

An electrocardiogram made shortly after admission demonstrated a low T₁, an absent R₄ and a slightly inverted T₄ (IVF). At this time

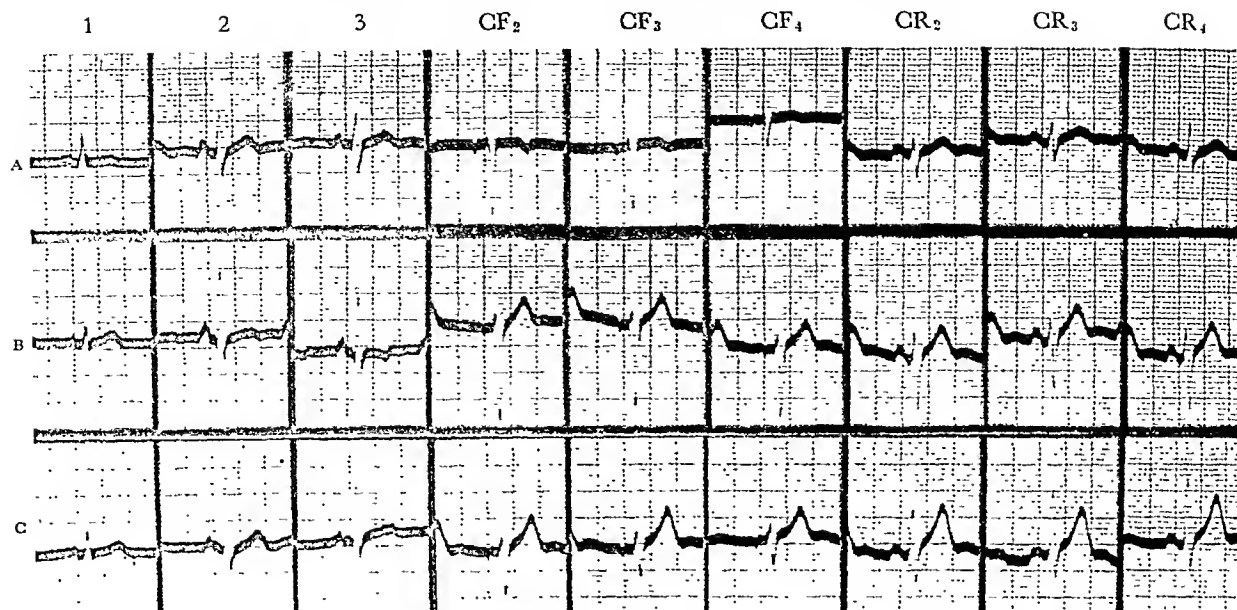


FIG. 8. Case IX. A, obtained on admission in the supine position; B, recorded at the same time in the upright position; C, recorded after recovery in the supine position.

the patient was reexamined in the erect position and Hamman's sign was at once apparent; the heart sounds were louder and the left cardiac border could be percussed without difficulty. An x-ray of the chest confirmed the impression of spontaneous pneumothorax on the left with approximately 10 per cent collapse. Lateral radiographs demonstrated air in the mediastinum.

Additional electrocardiograms were made including CF_2 , CF_3 , CF_4 , CR_2 , CR_3 and CR_4 in the supine, prone and erect positions. The CF leads made in the supine position showed small to absent R waves and flat to inverted T waves. In the erect and prone positions the T waves in all the CF leads became erect although the R waves remained small. T_1 which had previously been very low became of normal amplitude and T_3 became inverted. The T waves derived from the CR leads were somewhat lower in the supine position than in the erect. However, the CR leads were within the normal range in any position. (Fig. 8.)

When the mediastinal emphysema and the pneumothorax had cleared the tracing became normal in all leads and in all positions. It was then essentially similar to the curve obtained originally in the erect position. The R waves in the CF leads remained small.

Comment. The T wave inversion in this case resembled that found in children and in Cases 11 and 111 described earlier. The

greatest degree of inversion was present in CF_2 while the CR leads were normal. The cause for this phenomenon was doubtless the physical presence of air in the mediastinum and in the pleural space lying between the heart and the chest wall on the left. This produced a region of diminished conductivity and interfered with the normal inscription of the electrocardiogram. When the patient was in the erect or prone position and air was no longer trapped between the heart and the exploring electrode, part of the non-conducting medium was removed and the tracing became essentially normal. This is in complete accord with the experimental demonstrations of Katz and his associates⁸ who concluded that "alterations in the relation of various regions of the heart to the good electrical conductors and alterations in the location of the latter are important factors in modifying the ordinary electrocardiogram."

The interference phenomenon was apparently less important when the right arm was used as the indifferent electrode than the left leg. The reason for this is not readily apparent but must be associated with the different pathways normally utilized to complete the electrical circuit in the various leads.

COMMENTS

The cases presented in this study have demonstrated the fact that at one time or another they all exhibited grossly abnormal electrocardiograms without heart disease that could be otherwise proven. The cause for the abnormalities was apparent in some and quite obscure in others. Where it could be determined that the T wave inversion was the result of spontaneous pneumothorax with mediastinal emphysema or constituted persistence of the juvenile pattern, the diagnosis was neither sinister nor difficult to make. On the other hand, in the other cases presented no definite diagnosis could be made or sustained. It is impossible to state at this time that they did not represent instances of preclinical heart disease which will become manifest with the passage of time. Nevertheless, with the exception of the electrocardiogram it was impossible to make a diagnosis of organic heart disease by physical examination or by any other means now at our disposal.

It then becomes a question whether the unsupported inscription of the electrical phenomena of the heart as interpreted by present methods can be implicitly depended upon to make a diagnosis of heart disease or whether it should be treated as merely one diagnostic procedure to be integrated with other findings. In view of the fact that our electrocardiographic limits of normal have been constantly expanded it seems safer at this time to reserve the diagnosis of organic disease of the heart for those cases in which the condition can be proven by additional means. Doubtless, at some time in the future the limits of normal will be more clearly defined and additional refinements of technic will have been made so that electrocardiographic findings will carry greater diagnostic weight.

This is suggested in those cases considered to represent persistence of the juvenile pattern. In these individuals abnormalities were present only in the CF leads while the CR leads were normal. In a similar manner the case of spontaneous pneumothorax demonstrated abnormalities limited to the

CF leads and then only when made in the supine position. Additionally, the value of serial tracings is emphasized. It will be recalled that with few exceptions it was possible to obtain essentially normal curves after the passage of time following exercise or when made on an empty stomach.

Accordingly, when abnormal curves are encountered without adequate support of additional findings, the following extensions of electrocardiographic technic are recommended: (1) Electrocardiograms made with multiple chest leads employing the several standard indifferent points;⁶ (2) tracings recorded with the patient in various positions; (3) tracings made at various hours of the day, before and after meals; (4) curves obtained before and after exercise and (5) serial tracings made over a period of weeks or months.

It is entirely probable that a carefully individualized approach may serve to demonstrate normal curves in many subjects having functional or non-cardiac electrocardiographic anomalies.

SUMMARY AND CONCLUSIONS

Nine instances of gross electrocardiographic abnormalities are described in individuals without demonstrable disease of the heart. The deviations were greatest in the thoracic leads.

Essentially normal curves were eventually obtained in most of the subjects by various means.

The cause for the anomalies was demonstrated in several of the patients but remained obscure in the remainder.

It is suggested that refinements in electrocardiographic technic may serve to demonstrate normal electrocardiograms when ordinary methods indicate a state of disease.

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Asymptomatic Heart Disease^{*}

Observations Made during the Early Recruiting Period for Navy and Marine Enlistments

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THE opportunity of investigating cardiovascular disease entirely free from the elaborate overemphasis of a patient's subjective symptomatology is, unfortunately, not common. Individuals only come to a cardiac clinic or to a doctor's office for relief of subjective complaints; occasionally, unsuspected heart disease is discovered in patients being examined for other conditions. Applicants for life insurance are sometimes found with asymptomatic cardiovascular disturbances but no large groups of such patients are encountered in private or hospital practice.

This report is concerned with a special group of asymptomatic men and boys, all with one type of cardiovascular disease or another, who were discovered during the enlistment examination for admission into the Navy or Marine Corps during the early months of the recruiting period following Pearl Harbor. From December 8, 1941 until July 15, 1942, about 1,900 candidates were referred from the recruiting offices to the cardiac service of a certain naval hospital for diagnosis; of these, 350 were selected for special study because they were without symptoms or subjective complaints of any kind. As a by product of the mobilization of man power for war this group of individuals with asymptomatic heart disease seemed worthy of special investigation.

It must be admitted at the very outset that the choice of these patients for study was accomplished with some difficulty and

only after considerable individual questioning. The patriotic appeal for enlistment after the Pearl Harbor disaster swept into every recruiting office tens of thousands of youths and older men, all anxious to get into the Navy or Marine Corps. Many knew that they had disabilities of one kind or another but each one cherished the hope that he might, however, be accepted. This led naturally to the denial of previous medical conditions and to convenient memory lapses in regard to anything in the past history which could be considered disqualifying. When such disabilities were subsequently discovered on physical examination, most of the candidates good-naturedly admitted the discrepancies in their stories and said that it was only the desire to serve their country that caused them to make mis-statements.

There was a large group of candidates for enlistment, roughly about one-eighth of the total, who expressed surprise upon being told that they were unable to pass the general physical examination. Many of them were sent to the various special clinics for more intensive study and diagnosis as well as for evaluation of discovered defects. The cardiovascular service, as indicated before, received about 1,900 of these individuals. A simple breakdown of the figures shows that about one-half (825) denied knowledge of previous cardiovascular conditions; of these, 243 finally admitted a history of rheumatic fever either

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by name or symptoms (growing pains, St. Vitus dance, acute arthritis, heart fever) and 188 on close questioning confessed to either present or past symptoms of myocardial insufficiency (dyspnea, palpitation, heart pain or congestive failure). The remaining 394 individuals were again screened from the point of view of honesty, reliability and cooperativeness; forty-four were rejected, leaving the group of 350 which forms the basis of this report.

The ages of these candidates covered the years between seventeen and fifty-one; the general average was twenty-six. The largest group was in the twenty-three year class; the smallest in the forty-seven, forty-nine, fifty and fifty-one year classes which had three each. Of the 350 selected for the study, 336 were white, twelve were negroes and there was one American Indian and one Chinaman. As a group they represented a cross section of men in the average American city; nearly every trade, profession and type of work was found in the statistical data and the educational background was higher than the general population index. All but fifty-four were high school graduates and of these only twelve had less than two years of secondary school education. These latter facts are mentioned only to suggest that the group as a whole was intelligent and understanding; this background is necessary in giving the proper evaluation to their previous history and absence of cardiovascular symptoms.

A summary of the five general disturbances of the heart and blood vessel system which were found in this asymptomatic group is presented in Table I.

The distribution of these conditions is interesting; the number of cardiac irregularities is high compared with the incidence of arteriosclerosis. It is no surprise to find that arteriosclerosis may be productive of no symptoms; patients with advanced vascular degenerative changes may be entirely symptom-free. Irregularities of the heart, on the other hand, are frequently associated with considerable cardiac consciousness, sometimes out of proportion

to the actual hemodynamic disturbance created, for example, by premature contractions. Valvular heart disease and hypertension account for more than one-half of the disabilities found and simple cardiac hypertrophy for about 7 per cent of these

TABLE I
CARDIOVASCULAR CONDITIONS FOUND IN ASYMPTOMATIC GROUP

Valvular heart disease.....	169
Hypertension.....	89
Irregularities of the heart.....	55
Simple hypertrophy.....	26
Arteriosclerosis (premature).....	11
Total.....	350

asymptomatic patients. It may be profitable to consider each of the five major groups in some greater detail.

VALVULAR HEART DISEASE

Valvular heart disease is ordinarily associated with a symptom complex which is well embroidered with a number of subjective complaints, both great and small. While the various valve disorders have more or less specific and characteristic symptoms, there are certain complaints common to all. Heart pain and heart consciousness are the most frequent while the patient is at rest; palpitation and dyspnea occur after exercise.

The relative distribution of the valve lesions found in this asymptomatic group is shown in Table II. In most of the patients the pathologic condition was chiefly localized to one valve but in those instances in which more than one murmur was heard only the predominating lesion was given.

Mitral Insufficiency. In the group of candidates with mitral insufficiency six had hearts graded as greatly increased in size by x-ray mensuration, fourteen moderately enlarged and nineteen slightly enlarged; the remaining fifty-four had hearts of normal size. The murmurs received the following grades: sixteen candidates had grade 4 murmurs, thirty-two had grade 3, twenty had grade 2 and twenty-five grade 1. There was no relationship between loudness, intensity and distribution of the systolic

murmur compared to the size of the heart. Three men with grade 1 murmurs had the largest hearts and eleven with grade 4 murmurs had normal-sized hearts. Of the six patients with greatly enlarged hearts only three had a left axis deviation by

TABLE II
DISTRIBUTION OF VALVE LESIONS

Mitral insufficiency.....	93
Mitral stenosis.....	41
Aortic insufficiency.....	22
Aortic stenosis.....	9
Congenital lesions.....	4
Total.....	169

electrocardiographic examination; the fourteen with moderately enlarged hearts showed but one left axis deviation. The group of nineteen with slightly enlarged hearts showed three left axis deviations and the remaining fifty-four normal-sized hearts had two left and five right axis deviations.

No correlation curves could be established either between the length of the P-R interval and the size of the heart or the grading of the murmur. All possible combinations of these three factors were discovered. Abnormally long P-R intervals up to 0.28 second were found in grade 1 murmurs and normal-sized hearts; all of the patients with grade 4 murmurs and enlarged hearts had a P-R interval under 0.20 second. Finally, no relationship was found in regard to the standard exercise tolerance test with either the grading or the murmur, size of the heart or ECG changes. Candidates with the largest hearts and loudest murmurs seemed to do about as well as those with normal-sized hearts and grade 1 murmurs; in fact, the poorest showing in the test was made by seven youths all with grade 1 murmurs and normal sized hearts.

In summary, it would appear that in patients with asymptomatic mitral insufficiency no obvious relationship exists between (1) loudness, duration and distribution of the systolic murmur; (2) size of the heart; (3) electrocardiographic changes and (4) the exercise tolerance test. Statistically, this lesion was the most common valvular

disease and it accounted for more than one-half of all the murmurs discovered; it was more than twice as frequent as mitral stenosis, four times more frequent than aortic insufficiency and ten times more common than aortic stenosis.

Mitral Stenosis. Forty-one of the 350 candidates studied had presystolic murmurs; this is about 12 per cent of the whole group and 25 per cent of those with valvular lesions. Those with presystolic murmurs received the following grades: five individuals had a grade 1 murmur, twenty-two had grade 2, eight had grade 3 and six grade 4. X-ray mensuration showed that twenty-six had no change in heart size, five had a slight increase, six a moderate increase and four had greatly enlarged hearts. ECG studies showed eight patients with P-R intervals longer than 0.20 second, six with simple right axis deviation, ten with a combination of P-R delay, axis deviation and other abnormalities like a QRS spread beyond 0.12 second, S-T changes or T wave variations. Seven individuals had normal tracings. The standard exercise test was well performed by twenty-nine, fairly well by six, poorly by five and badly by one.

Attempts to plot correlation curves between the four diagnostic criteria (murmur grade, size of heart, ECG changes and exercise test) were more successful here than in the group of patients with mitral insufficiency. In general it was found that the candidates with grade 4 murmurs had larger hearts, more electrocardiographic changes and a poorer exercise tolerance than in the other murmur grades; beyond this generalization there was considerable individual variation. One man with a grade 1 presystolic murmur, for example, had the largest heart in the entire group, a good exercise test and no ECG changes; another had a grade 3 murmur, a small heart, a fair exercise test and considerable ECG abnormality (P-R interval delayed to 0.28 second, QRS of 0.14 second, with slurring and right axis deviation). Still another had a grade 2 murmur, slightly enlarged heart, normal ECG and a poor exercise test. One

gained the impression, however, that as a group mitral stenosis in its asymptomatic stage is productive of more objective cardiac disorders than mitral insufficiency.

Aortic Insufficiency was discovered in 22 of the 169 valvular cases or about 13 per cent. Grading of the diastolic murmurs seemed to present more difficulty to the examiners than any other type of murmur and there were many honest differences of opinion in regard to the following distribution of the murmur grade classification:* seven candidates had a grade 1 diastolic murmur, four had grade 2, eight had grade 3 and three had grade 4. As to heart size eleven had normal measurements, six had a slight increase in size, three a moderate increase and two had marked enlargement of the cardiac x-ray. The electrocardiographic studies showed twelve with normal tracings, six with simple left axis deviation and five with miscellaneous defects in addition to left axis deviation. The exercise tolerance test was well performed by sixteen, fairly well by two and poorly by four.

The correlation curves here showed only two significant findings: First, increase in heart size was accompanied by left axis deviation of various degrees not necessarily to the same extent. The largest heart had a moderate left axis deviation compared to a moderately enlarged heart which had a maximum left axis deviation. The second finding was a close coincidence between heart size and exercise tolerance; the larger the heart the poorer the effort response. There was an interesting relationship between the grade of the murmur and the three other diagnostic criteria plotted as a single curve; increase in the grading of

* Many of these patients were studied by simultaneous electrocardiographic, polygraphic and heart sound recordings made at the naval hospital. The timing of the murmur rarely caused any difficulty but the qualities of pitch, intensity and duration cannot be determined from phonocardiographic tracings made by the conventional apparatus. The special equipment used at the Adler Heart Sound Laboratory to produce phonograph records of heart sounds and murmurs for teaching purposes does, however, show these qualities and many of the candidates received a special work-up through the courtesy of the Louis Adler Cardiovascular Research Fund.

these three factors also multiplied their unit value. Thus, a grade 1 diastolic murmur might be unassociated with any other finding while a grade 2 murmur might have either some enlargement of the heart and ECG abnormality or a decreased exercise tolerance. A grade 3 murmur might have a combination of any two of those first mentioned and grade 4 would probably have all three. It was the correlation trend in this curve which made the proper evaluation of the murmur grading so important in the original examination and this explains why so much attention was devoted to the qualities of the diastolic murmur.

Aortic Stenosis. Only nine cases of aortic valvular stenosis were discovered; these represent but 6 per cent of the valvular lesions found and only 2.5 per cent of the total number of cardiac individuals in the asymptomatic group. The number seems small compared to the general incidence of aortic stenosis and the other valvular diseases seen in the cardiac clinic; perhaps aortic stenosis is less asymptomatic and more productive of subjective complaints than other lesions.

A breakdown of the figures shows that of the nine patients three were classified as grade 1 systolic murmurs, two as grade 2, two as grade 3 and two as grade 4. X-ray mensuration showed five to be of normal size, one slightly increased, three moderately increased and none markedly increased. The electrocardiograms revealed seven normal tracings, one left axis deviation and one intraventricular block with a QRS of 0.16 second. The exercise tolerance results indicated six with good response, one with fair response, two with poor response and none with bad response.

This group was too small to develop any significant trends in the correlation curves but there was a suggestion that some relation existed between heart size and exercise tolerance; the three moderately enlarged hearts all had less than normal effort response.

Congenital Heart Disease. Four candidates were diagnosed with congenital lesions

because of the character, timing and quality of the murmurs which were discovered. Two patients had continuous low pitched rumbling murmurs heard throughout the cardiac cycle with maximum intensity over the upper end of the sternum; one patient appeared to have a septal defect and the other a possible aneurysm of the pulmonic artery with an open ductus arteriosus. These patients form the subject of a paper to be published later.¹

A review of all these patients with valvular disorders shows that correlation curves obtained by plotting (1) type, quality and intensity of the murmur expressed in terms of grading from 1 to 4; (2) x-ray mensuration of the heart; (3) electrocardiographic and (4) functional response to exercise can be obtained in certain forms of asymptomatic valvular heart disease. Both mitral stenosis and aortic insufficiency show one or more such curves; aortic stenosis has a tendency to follow a coincident curve between heart size and exercise tolerance. No curves could be obtained in the study of mitral insufficiency although these individuals formed the largest group with valvular heart lesions.

HYPERTENSION

There were eighty-nine candidates for enlistment who had high blood pressure without symptoms or previous knowledge of the condition. The group divided into subclasses consisting of 10 mm. differences in systolic blood pressure is presented in Table III. The diastolic levels presented no problems and they are not considered here.

There are many clinical examinations and laboratory tests which can be made in the study of hypertension; only seven were selected for expediency and for economy of time, material and labor. These were: (1) clinical appraisal of the heart—rate, rhythm and murmurs; (2) x-ray mensuration; (3) electrocardiographic study; (4) exercise tolerance; (5) examination of the retinal arteries; (6) urinalysis and (7) other obvious pathologic conditions.

While the patients were classified into the

various groups given in Table III in order to show distribution of the systolic levels in 10 mm. differences, it was found that no significant trends in the correlation curves were obtained in the 10 mm. subdivisions so that this study was made by considering

TABLE III
DISTRIBUTION OF THE SYSTOLIC BLOOD PRESSURE LEVELS
IN THE HYPERTENSIVE ASYMPTOMATIC GROUP

	Cases
150 to 160 mm. Hg.....	31
160 to 170.....	27
170 to 180.....	18
180 to 190.....	7
190 to 200.....	2
200 to 210.....	3
210 to 220.....	1
Total.....	89

groups with 20 mm. differences. Thus, the first two groups with pressures from 150 to 170 are considered together, the third and fourth groups with pressures from 170 to 190 and the fifth and sixth groups with pressures from 190 to 210 are combined. The single individual with a pressure from 210 to 220 will be considered alone.

There were fifty-eight candidates referred for examination who had systolic blood pressure levels from 150 to 170. Only three of them were found to have cardiac disturbances (two had systolic murmurs and one had tachycardia). Five had enlargement of the heart; seven had ECG changes (delayed P-R interval in two, left axis deviation in four and wide QRS in one). Exercise tolerance was poorly performed in three. Funduscopy showed five with retinal artery changes. Urinalysis was abnormal in one (albumin present). Four had other conditions (one migraine, 1 gallbladder disease, one possible pulmonary tuberculosis by x-ray findings and one early hyperthyroidism).

In considering this group no correlation curves could be determined in plotting the seven diagnostic criteria against the various pressure levels or against each other. The group was, however, large enough to make certain generalizations: First, systolic blood pressure levels up to 170 have a minimum of objective pathologic disturbances and

secondly, no relation exists between the early types of disturbances as they tend to develop.

In the next group with pressures from 170 to 190 there were twenty-five candidates. Five had definite cardiac disturbances (two with gallop rhythm, two with systolic murmurs and one with tachycardia). Eleven had enlargement of the heart; nine had ECG changes (delayed P-R interval in three, five with left axis deviation and one with a bundle branch disorder). Sixteen had poor exercise tolerance tests; ten had retinal artery changes; five had abnormal urinalysis; four had other conditions (diabetes, one; possible gastric ulcer, one and chronic arthritis, two). Eleven individuals had no discoverable disorders.

The correlation curves in this group showed several significant trends: (1) a drop in the exercise tolerance tests occurred most commonly; (2) enlargement of the heart is the next most common finding; (3) changes in the retinal arteries come next in frequency; (4) ECG changes occurred in less than one-third of the patients; (5) cardiac disturbances and renal damage were found in only one-fifth of the group; (6) enlargement of the heart and ECG changes follow a coincident curve; (7) all of the patients with renal damage had retinal artery changes; (8) a poor exercise test may occur independently of any other finding but every patient with objective evidence of pathologic disorders had a poor effort response.

In the third group with pressures from 190 to 210 there were only five patients. Of these two had cardiac disturbances (gallop rhythm) and four had enlargement of the heart. All five had ECG changes (left axis deviation and one with T_1 iso-electric). Exercise tolerance was poorly performed in all patients; four had retinal artery changes, one very severe. Two had urinary evidence of renal damage and one had another condition (chronic pancreatitis).

This series is too small to draw anything but the general impression that systolic blood pressures in these higher levels is

associated with considerable objective pathologic conditions measured in the terms of the seven diagnostic criteria employed in the examination.

The single individual with a pressure in the 210 to 220 group had gallop rhythm, some enlargement of the heart, slight left axis deviation, fair exercise test, moderate hypertensive retinopathy and no other condition except a marked psychosomatic background which, however, did not lead to any symptoms referable to the hypertension.

In reviewing the data of the entire asymptomatic hypertensive group a few interesting observations may be made: Perhaps the most important is the fact that high levels of blood pressure may develop without subjective symptoms of any kind; this stands in contrast to the host of embellished complaints suffered by many patients with hypertension. Headaches, dizzy spells, "black outs," giddiness, nausea, vomiting, weakness, tremulousness, numbness and visual disturbances are but a few of the symptoms which cause such patients to seek medical attention. Every one of these patients denied symptoms of any kind, past or present.

The second observation is that objective pathologic conditions as the result of or associated with high blood pressure start to develop in significant trends when systolic levels rise above 170. Most of the patients with pressures below 170 had no cardiovascular changes while most of those with pressures above 170 had one or more abnormalities. In this series 170 seems to have been the critical dividing point of the two groups and this figure is of considerable interest in relation to the findings in psychosomatic hypertension.²

IRREGULARITIES OF THE HEART

Disturbances of cardiac rhythm were discovered in fifty-five patients; these were classified as shown in Table IV.

Extrasystoles. Electrocardiographic studies of these twenty-seven individuals showed the ectopic focus for the premature beats to have been in the ventricles in

eighteen patients, in the auricles in six, in the junctional area in two and one had a bifocal (auricle and ventricle) extrasystolic pattern. Considered in terms of frequency four had one or less premature beats per minute, eleven had from two to

TABLE IV

ASYMPTOMATIC IRREGULARITIES OF THE HEART	
Extrasystoles.....	27
Tachycardia (over 110).....	19
Auricular fibrillation.....	6
Heart block (complete).....	2
Heart block (incomplete).....	1
Total.....	55

three, five had from three to four, two had from four to five, three had from five to six and two had more than six extrasystoles per minute. The group as a whole was singularly free from cardiovascular disease. Only one of the twenty-seven had an enlarged heart and two had apical systolic murmurs. All had good exercise tolerance curves; all had normal blood pressures and there was no evidence of any other abnormal condition.

All of these individuals were symptom-free; this is interesting since the most common cause of heart consciousness and palpitation which occurs without effort is premature contractions. Strictly speaking, it is not the extrasystole which is responsible for the sensation or the awareness of the disturbance in the rhythm of the heart but the sinus beat following the ectopic one. Since the extrasystole is premature, it causes contraction of the left ventricle before it is completely filled; if it occurs very early in diastole, there may be insufficient blood in the ventricle to open the aortic valves. The refractory period which follows the premature contraction is usually much longer than the normal diastolic filling period, and the next sinus beat is thus accompanied by a greater volume output, sometimes as much as 80 per cent greater. This pulsation is transmitted throughout the entire arterial tree and subjective symptoms will arise in any tissue or organ which may be neuroreceptor-sensitive to

increased systolic pressure and blood volume changes.

Such hemodynamic disturbances are not confined to the extrasystolic arrhythmias; they may also occur in auricular fibrillation and in incomplete heart block. The condition may be and usually is productive of many subjective complaints. Since all of these patients were asymptomatic, they were more carefully studied by graphic registration of the electrocardiogram and simultaneous polygrams of the radial pulse. Of the twenty-seven all but three had the effective type of premature contraction, i. e., the ectopic beat occurred late enough in diastole to permit the aortic valves to open and the extrasystole was transmitted through the arterial system as a small premature beat. This type of premature contraction is ordinarily not perceived by the patient since the hemodynamic disturbance is minimal.

The other three candidates had ineffective premature contractions, i. e., the ectopic beat is so premature that there was insufficient blood present in the left ventricle to open the valves and no pulsation was transmitted to the arteries. In spite of the pressure changes and volume output of the next normal beat none of the three were aware of the disturbance even after it had been pointed out to them. It is these three who are interesting in the discussion of asymptomatic heart disease and they will be considered later in relation to the psychosomatic phenomena of cardiovascular disturbances.

Tachycardia. Nineteen candidates had persistent pulse rates of 110 or over. Three were found to have increased basal metabolic rates (plus 22 to 35 per cent) and one had an x-ray of the lung which was suggestive of reactivated tuberculosis. The remaining fifteen had no discoverable extracardiac cause for the rapid heart action. All were of the parasympathetic habitus described by Wolffe; they also might be considered in the Oppenheimer classification of neurocirculatory asthenia. A better concept suggested by Drcifuss is

based upon the psychosomatic evaluation of the whole condition which is now loosely labeled "cardiac neurosis" or "effort syndrome." This problem has been previously discussed³ as one of the major subdivisions of psychosomatic heart disease. After more than five years of experience with these patients in relation to the military service it was the author's opinion that they were unfit for combat duty and the entire group of nineteen was disqualified for enlistment.

Auricular Fibrillation. Six candidates had grossly irregular pulses; all proved to be auricular fibrillation by electrocardiographic examination. Five were slow fibrillators with apical rates averaging from 54 to 76 per minute; these had no pulse deficit and were more or less well compensated. On physical examination no murmurs were heard, the hearts were not enlarged and the blood pressures were within normal limits. The exercise tolerance test was fairly well performed by all. None had a history of rheumatic fever and all denied previous cardiac disability.

Like extrasystolic arrhythmia auricular fibrillation may be productive of a variety of subjective complaints and symptoms; these are due to the irregular blood flow, volume changes and pressure alterations. All these factors become exaggerated after exercise since the pacemaker mechanism no longer controls the rate of ventricular contraction. At rest most slow fibrillators have no circulatory deficiency but when the demand for greater volume output occurs, various degrees of decompensation develop. When the so-called idiopathic ventricular rates are within the normal frequency range, work may sometimes be performed with little loss of functional capacity and one is often astonished at the magnitude of the physical tasks performed by such patients without symptoms of any kind.

When the ventricular rates are rapid and over 100 per minute a pulse deficit occurs. The pulse deficit in auricular fibrillation presents the same hemodynamic phenomenon as the premature contractions do in the extrasystolic arrhythmias. Contraction

of the empty or poorly filled left ventricle is not accompanied by a pulsation in the arterial tree; the heart contracts but no radial pulse is felt. As the ventricular rate rises in auricular fibrillation the pulse deficit increases and in the rapid rates seen in delirium cordis the ventricular contractions may rise to 180 or 200 with a radial rate of 90 or less. The pulse deficit in some of these patients may be as much as 100 per minute.

Experiments have shown that under such circumstances the per minute volume of blood delivered by the left ventricle to the arterial system may be reduced to 85 per cent of normal and congestive failure rapidly develops. Between the well compensated non-deficit type of auricular fibrillation and the stage just described is a large ill defined group of patients who carry on moderate activity with a minimum of subjective discomfort.

One of the six candidates with auricular fibrillation was one of this group. He had a ventricular rate of 108 and a radial rate of 88; the deficit here was 20. He had a slightly enlarged heart and a grade 3 systolic murmur could be heard over the mitral area. The ECG showed a left axis deviation in addition to fibrillation. The blood pressure was 118/66. The exercise test was fairly well performed and he had no signs of congestive failure although the venous pressure appeared to be increased. This patient was twenty-four years old and had been working for more than two years as a helper on a parcel delivery service, a job which required considerable labor and long hours. He was intelligent and alert but was completely unaware of any cardiac disability; the author had seen similar cases previously.

Asymptomatic auricular fibrillation is most likely to occur in those patients who do not have a history of rheumatic fever or valvular heart disease, particularly mitral stenosis; it is seen most frequently in patients with spontaneous or idiopathic auricular fibrillation and the condition may only be discovered by chance unless one or more of the intravascular complications of

the condition occurs (embolization, infarction or cerebral accidents).

All of the six candidates for enlistment were rejected as the disturbance, even though it may be asymptomatic, is sooner or later a serious cardiac disability. The prognosis in any given case is quite unpredictable; certain individuals have been known to pursue perfectly normal lives for many years. Other individuals may break down abruptly for no obvious reason. As a group they are poor military risks even for limited duty.

Heart Block. (Complete auricular and ventricular dissociation). Two candidates were discovered to have complete heart block, one with a ventricular rate of 44 and the other 60 per minute. The first case was suspected at the original recruiting examination because of the low pulse rate; the patient said he always had a slow pulse and he remembered as a child being told that his heart was not beating as fast as normal but he denied symptoms of any kind and had followed his work as an accountant without difficulty. He had been examined at the age of twenty-three and passed for life insurance; his present age was twenty-five.

On examination the heart sounds were of good tonal quality; no murmurs were heard. X-ray showed no change in heart size. His blood pressure was 140/88. ECG showed a regular auricular rate of 74 and a ventricular rate of 44. There was no axis deviation but the QRS was spread to 0.12 second. The precordial leads CF_3 , CF_4 and CF_5 showed a T wave inversion. The exercise test was fairly well performed as far as dyspnea was concerned but no change occurred in the radial rate.

The evidence here suggested a congenital type of A-V dissociation; ordinarily there is a compensatory hypertrophy of the left ventricle to meet the demand for a greater volume output than that which can be delivered at the slow rate of 44. In certain cases of juvenile complete block, enlargement of the heart with corresponding left axis deviation may develop rather late. In

this patient a satisfactory adjustment had apparently been made in his hemodynamic balance and no secondary changes had as yet appeared.

The second man was more interesting. He was sent to the cardiac clinic for study because his heart rate did not speed up after the exercise test; from this single finding a presumptive diagnosis of complete heart block was made notwithstanding the "normal" pulse rate of 60. He was thirty-one years old, a chemistry teacher, more or less active in athletics, with a negative history except for two attacks of tonsillitis, an appendectomy and a fractured humerus as a child. He denied previous cardiac disability of any kind and had passed successfully several physical examinations for insurance and civil service. The heart was not increased in size by x-ray. The heart sounds were of good tonal quality and regular. No murmurs were heard. Blood pressure was 134/90 and ECG showed an auricular rate of 78 and a ventricular rate of 60; the QRS was at the upper limit of normal (0.10 second) but there was no other abnormality either in the limb or precordial leads. The exercise test was fairly well performed except for slight dyspnea and no change in the pulse rate.

With the diagnosis established, a closer examination revealed other signs of A-V dissociation: asynchronous pulsations in the carotid arteries and jugular veins, absent vagal respiratory changes in the pulse rate and changes in the first heart sound from beat to beat. Complete heart block with idioventricular rates in the 60's and 70's are not as uncommon as the earlier writers have reported. From 1925 to 1934 the author was fond of demonstrating to his students the case of a man with a pulse rate of 72 who had complete A-V dissociation with considerable myocardial damage; he worked as an elevator operator in the hospital for nearly twelve years with a minimum of cardiac disability; he has reported other such cases with high idioventricular rates.⁴

As indicated previously many patients with complete heart block are usually free

from symptoms while at rest; it is only when ventricular output fails to meet circulatory demands that signs of failure develop. Dyspnea and heart pain occur first; pulmonary congestion and peripheral edema occur later. When idioventricular rates become very slow, from 30 to 20 per minute, cerebral anoxemia is the predominating symptom with episodes of fainting and unconsciousness; this was described nearly a century ago by Stokes and later by Adams. With the higher ventricular rates, from 56 to 76, many patients may, however, be free from symptoms even after considerable exercise but sooner or later the inadequate output from the heart will make itself felt. Such individuals, of course, make poor military material and must be rejected even though their present cardiovascular status appears competent.

Incomplete heart block with an occasional missed ventricular beat was found in one candidate. He was referred for cardiac investigation with a diagnosis of extrasystolic arrhythmia. Without ECG study the two conditions cannot be distinguished; the compensatory pause following the premature contraction is recognized by the examiner and sometimes the patient as a "skipped beat." A ventricular beat which is blocked at the A-V node appears also as a missing or dropped beat between two normal beats. Whereas extrasystoles are not ordinarily disqualifying for enlistment, incomplete heart block represents a type of cardiac disease which is sufficient to reject a candidate.

This man was a thirty-three year old carpenter who was anxious to get into a Seabee unit. He denied a rheumatic history and had no previous cardiac disability; he had been working at his trade for about fifteen years without a single day's union sick benefits. On physical examination the heart was somewhat increased in size by X-ray. The heart sounds were of fair tonal quality, regular, 76 with four to six skipped beats per minute. These skipped beats were not increased by exercise and they per-

sisted after a period of bed rest. A soft systolic murmur, grade 2, was heard at the apex but this was considered functional since it had many postural changes and disappeared after exercise. The ECG showed a P-R interval prolonged to 0.26 second, the QRS was normal but there was slight left axis deviation. ST and T were normal. The precordial lead CF₄ was normal. Every twelfth to fifteenth P wave was not followed by a QRS complex; there was no Wenckebach effect.

The candidate was not conscious of the skipped beat and the exercise test was well performed. This type of incomplete heart block with a 12:11 rhythm usually does not remain in this pattern; either the ratio increases to the more familiar 4:3, 3:2 or 2:1 rates or the phenomenon of the blocked beat entirely disappears, leaving the patient with a prolonged P-R interval or so-called first degree heart block. This man was seen three times over a period of eight weeks with no change in the general electrocardiographic pattern. In spite of all of the examinations which he had gone through and even though he had been the focus of considerable medical attention, he was still asymptomatic and could not identify the skipped beats when they occurred. He represents the minimum in psychosomatic reaction.

In summary, of the eighty-five candidates referred for irregularities of the heart only the group of twenty-seven with premature contractions were accepted. The others all had cardiac disturbances which were disqualifying although entirely asymptomatic. Of special interest here was the group of fibrillators and their general freedom from cardiovascular complaints even after the effort tolerance tests.

CARDIAC HYPERTROPHY

Simple enlargement of the heart was found in twenty-six candidates; the diagnosis was chiefly made by x-ray mensuration. A routine recruiting chest film was made upon each applicant for enlistment in both the Navy and Marine Corps; this

was done largely to screen out tuberculosis suspects. From time to time other conditions were discovered in the chest films and these patients received additional x-ray examinations. Twenty-one of the candidates were picked out this way and referred to the cardiac clinic for further study. The remaining five were discovered by the examining physicians at the enlistment offices; all of these patients either had an apex impulse outside of the mid-clavicular line, or below the fifth interspace or both.

On detailed examination none of the group had murmurs of any kind. The ECG study showed seven with left axis deviation, one with early right axis deviation, two with prolonged P-R intervals (0.22 and 0.26 second), one with an intraventricular block pattern (QRS delayed to 0.14 second) and the remaining fifteen were within normal limits. The blood pressure was normal in twenty-three; the other three were 148/90, 150/88 and 154/94. The exercise tolerance test was well performed by eighteen, fairly well performed by three, poorly performed by three and badly performed by one.

No correlation curves could be drawn from the size of the heart, ECG findings, blood pressure or exercise tolerance curves. The only significant trend was in relation to heart size and left axis deviation; the seven patients with left axis deviation came within those having the ten largest hearts. The hypertensive patients only had moderately enlarged hearts but one had the intraventricular block pattern.

These candidates were closely questioned in regard to their participation in past or present athletics. There was a history of more than moderate athletic activity in fifteen of the twenty-six, moderate activity in seven and four said that they had not been interested in physical sports; in other words, twenty-two of the twenty-six had engaged in athletics in one degree or another. In view of the current discussion in regard to the so-called athletic heart this figure may perhaps be of some significance since it is the single most common factor found in the group with cardiac hypertrophy.

Cardiac hypertrophy of unknown origin has received the attention of many authors⁵ but in the cases reported nearly all of the patients have had severe symptoms. Levy and Von Glahn have recently published a series of ten fatal cases⁶ but there are other reports of individuals with "idiopathic" cardiac hypertrophy who have lived for a considerable period of time after discovery of the condition. The available literature says nothing, however, about the outlook of such patients who are without subjective symptoms of any kind.

In considering the eligibility of this group for military service many problems were discussed by the medical officers charged with forming a policy to be followed in such candidates. When simple enlargement of the heart existed without any other finding, i. e., electrocardiographic changes, hypertension, lowered exercise tolerance or other cardiac disability, the individual was accepted. Of the twenty-six only four, which was less than 15 per cent, were qualified for enlistment.

ARTERIOSCLEROSIS

Premature arterial changes were discovered in eleven candidates; this was about 3 per cent of the entire asymptomatic cardiovascular group. The diagnosis of premature arteriosclerosis was made when the degree of vascular change was inconsistent with the age period. The age distribution showed one candidate twenty-seven years old, one aged thirty, two aged thirty-four, one aged thirty-six, four aged thirty-eight, one aged forty and one aged forty-two.

The peripheral vascular examination was standardized for economy of time and labor; the following tests were recorded upon all patients of the vascular group who were referred for study: (1) palpation of the radials, posterior tibials, dorsalis pedis, temporals and any other available artery to determine rigidity, mineralization and other abnormalities; (2) blood pressure of the brachials, femorals and dorsalis pedis; (3) oscillometric readings of both arms and

legs; (4) x-ray visualization when mineralization was present or suspected; (5) funduscopy; (6) thermal changes of the feet; (7) color changes of the feet; (8) special x-ray films of the aorta and (9) when indicated, electrocardiographic studies.

A review of this data showed that the most common finding was increased rigidity and thickening of the radial arteries; this occurred in nine of the eleven patients. Tortuosity and thickening of the temporal arteries were found in six, retinal vascular changes in five, oscillometric abnormalities were discovered in the legs of three, thermal and color changes in two and x-ray visualization of the tibials was found in one. No significant trends could be determined from the correlation curves; the series was perhaps too small to show possible relationships. These patients required more laboratory investigation than was considered necessary for the enlistment examination; blood chemistry data in regard to cholesterol, N. P. N., sugar, chlorides, calcium and renal function tests would have made the study more valuable.

The three candidates with oscillometric changes in the vessels of the legs presented some interesting findings: Two had complete obliteration of the dorsalis pedis pulsations in both feet, both had color and thermal changes. One was a man of thirty-eight, the other was forty-two. Both denied peripheral vascular symptoms of any kind and it was only the dusky cyanosis of their feet which called attention to need for further study at the original enlistment examination. These patients stand in sharp contrast to the usual symptoms and complaints given by most individuals with vascular disturbances of the extremities; minor degrees of vascular change may be accompanied by considerable pain and disability. When the condition becomes as advanced as that shown by these two men, there is ordinarily a history of many years of pain and suffering. Asymptomatic peripheral vascular disease is sometimes picked up accidentally in the course of a general physical examination, but the experience

in most cardiovascular clinics is that the syndrome is not a silent one and most patients have subjective symptoms far out of proportion to the actual degree of circulatory impairment found.

While the youth of some of the candidates with vascular disease is perhaps unexpected, the actual number of individuals with premature arterial changes who were discovered was extremely small. The eleven selected are presented here because they were without symptoms or previous medical history; about forty-five other candidates with arterial conditions and with symptoms were also seen. Thus, a total of only fifty-six individuals of the many thousands who were examined for enlistment were found to have early vascular disease. These statistics are interesting in relation to the alleged increase in the number of young people with arterial diseases.

COMMENT

In considering these 350 individuals with cardiovascular disorders and without symptoms several interesting questions arise for which there are, perhaps, no acceptable answers. Indeed, some of the fundamental problems involved are not primarily cardiovascular at all but common to the entire pain receptor mechanism of the patient. Why were these candidates without pain and symptoms? With the heart admitted to be a specially sensitive organ why, for example, were 169 with valvular heart disease and fifty-five with irregularities of the pulse free from subjective complaints of any kind? With peripheral vascular disease as a painful and disabling condition, why did two of these patients with advanced arterial disturbances of the feet not have a single complaint? Again, hypertension is productive of many subjective symptoms but eighty-nine candidates with high blood pressure were symptom-free. Why? In short, what explanation can be given for the asymptomatic course of these various cardiovascular conditions and what is responsible for the lack of subjective response?

Less than a decade ago it would have been considered pure speculation to have attempted any explanation concerning the variability of sensory response to visceral stimulation, but some of the concepts of psychosomatic medicine have done much to clarify many of these confusing clinical phenomena. The heart as an organ entity (Wolffe) is peculiarly responsive to psychomotor stimuli and like the gastrointestinal and central nervous systems it may initiate somatic symptoms in a degree far out of proportion to the primary receptor mechanism stimulus. At the same time primary somatic stimuli arising within the heart itself as the result of a disturbed or pathologic physiology find a track into consciousness by way of the same or similar receptor system pathways. When the factors conditioning the common pathways are used frequently enough or when a pseudo-reflex develops in linking the autonomic and central nervous system via a sensitized tissue or organ, the subjective symptoms which develop are equally appreciated in consciousness regardless of whether the stimulus actually arose in the heart itself or whether the entire syndrome is extracardiac.

On the other hand, these pathways to consciousness may be poorly developed or physiologically blocked in certain individuals. There are a number of possible variants which can explain this phenomenon: (1) tissue injury does not produce a somatic stimulus; (2) the stimulus if produced is reduced on its way to consciousness; (3) a psychomotor stimulus from the same or different tissue using the same pathway modifies the somatic stimulus either by reduction or amplification; (4) the psychomotor stimulus may receive priority in consciousness; (5) any combination of the aforementioned may occur.

In addition to these factors which are chiefly related to the visceral organs without direct afferent sensory connections to the brain must be considered the individual's idiopathic threshold to painful stimuli (Libman). There is a paradoxical relationship between a patient's psychosomatic

response and his relative threshold to pain; in brief, while it is true that nearly all psychosomatics have low thresholds in the response to painful stimuli, not all persons with low thresholds are psychosomatic personalities.

Only relatively few of the candidates with asymptomatic heart disease were tested for pain threshold; time and circumstance did not permit the study that these patients merited but a group of sixty were selected at random during the course of the seven month-period covered by this report. They represent a fair sample of the various cardiovascular conditions already described. Of the sixty, fourteen had a low threshold for pain, forty-four were considered within the normal range of sensitivity and two had a high threshold. The fourteen with the low thresholds should have been symptomatic according to Reisman's theory but they were not. What combination of factors is responsible for this? Perhaps the answer will come from the vast research projects in psychosomatic phenomena now being stimulated as a result of the war.

In closing, let us now turn to a consideration of the more factual data of this report. A group of 350 individuals with various types of cardiovascular disease have been presented, none of whom had the usual or expected symptoms and complaints of patients suffering from these conditions. An opportunity was presented to study heart and blood vessel disorders from a purely objective point of view; the examiner was uninfluenced by what the patient said and the final opinion and diagnosis in each case was the result of physical findings alone. In evaluating these data certain correlation curves were attempted between various diagnostic criteria in order to present a more complete and accurate clinical picture of some common cardiovascular disorders.

Results in certain respects are confirmatory of impressions previously gained from cardiac clinic experience; statistically a number of generally held opinions are found to be true. When the series in individual conditions has been large enough,

significant trends have indicated important relationships in the development of cardiac syndromes. Taken together these data should prove to be helpful in diagnosis and evaluation of disabilities arising from heart and blood vessel disease.

SUMMARY

1. A group of 350 men within the age periods of seventeen to fifty-one discovered to have cardiovascular disease on examination for enlistment in the Navy and Marine Corps were studied because they were free from subjective symptoms of any kind. The opportunity for investigating asymptomatic heart disease has previously been limited to isolated cases. Since subjective complaints play such a great rôle in nearly every cardiac patient, this study is an attempt to evaluate the factual data in different forms of cardiovascular disturbances free from the usual psychosomatic background.

2. These men were classified into five general groups for purposes of comparative studies: (1) valvular heart disease; (2) hypertension; (3) cardiac irregularities; (4) simple cardiac hypertrophy; (5) premature vascular disease.

3. In valvular heart disease certain correlation curves could be obtained between heart size, type of murmur, electrocardiographic changes and exercise tolerance tests.

4. In the hypertensive group correlation curves were attempted between the clinical appraisal of the heart itself, x-ray mensuration, ECG, exercise tolerance test, funduscopy, urinalysis and other associated tests.

5. Cardiac irregularities included the

extrasystolic arrhythmias, tachycardia, auricular fibrillation, incomplete heart block and complete A-V dissociation. Only the group with premature contractions were accepted for enlistment.

6. Simple cardiac hypertrophy showed certain correlation curves which disqualified most of the candidates; only four of twenty-six were accepted.

7. The candidates with various types of peripheral vascular disease and other arterial disturbances were also disqualified although they were asymptomatic.

8. A possible explanation concerning the freedom from subjective symptoms and complaints in this group of 350 individuals is presented; the theory of development of psychosomatic phenomena in cardiovascular disease and its relation to the pain receptor mechanisms of the autonomic system are discussed.

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Significance of Electrocardiographic Changes in Rheumatic Fever^{*}

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CARDITIS is one of the major criteria by which rheumatic fever can be recognized. In determining the presence of carditis in any given case abnormalities in the electrocardiogram are often the sole objective findings of cardiac involvement. In the young adults who came under our observation at the Naval Hospital in Oakland, California and who were made the basis of this study, unequivocal evidence of carditis, such as cardiac enlargement, significant diastolic murmurs, acute pericarditis or congestive failure were not commonly observed during attacks of rheumatic fever. Subjective symptoms such as dyspnea and precordial pain are suggestive but not sufficiently clean cut for diagnosis. Systolic murmurs, because of their frequency in any febrile disease associated with tachycardia as well as in normal individuals, are difficult to evaluate. Systolic murmurs that appear while the patient is under observation for possible rheumatic fever, or are long, loud and varying but little with position or respiration are of more definite diagnostic value. Muffled heart sounds of poor quality are frequently heard but are difficult to evaluate. The changing quality of the heart sounds with improvement of the patient is often suggestive of cardiac involvement. The electrocardiogram must be relied upon to a large extent to determine the presence of carditis. This is true not only in the initial diagnosis but also to determine the presence of continued rheumatic activity or recrudescence. The

necessity for exercising the greatest care in evaluating minor electrocardiographic abnormalities must be re-emphasized, especially in view of the recent studies in service personnel^{1,2} that demonstrate the widened range of variants in normal individuals. The changes in the electrocardiogram to be described are not specific solely for rheumatic fever, but when present in this disease indicate involvement of the heart.

Based on several hundred cases of rheumatic fever personally observed the following points will be discussed: types of electrocardiographic abnormalities seen, diagnostic value of these abnormalities in unusual or subacute rheumatic fever, duration of the abnormalities, value of repeated electrocardiograms in assessing continued rheumatic activity or recrudescence (often present without other clinical or laboratory signs), absence or insignificance of electrocardiographic abnormalities in the presence of carditis and fixed residual electrocardiographic changes which are occasionally seen. Various types of abnormalities will be illustrated by case reports.

Partial Heart Block in Rheumatic Fever. It is well known that the most common abnormality noted in the electrocardiogram in rheumatic fever is a partial A-V heart block.³⁻¹⁵ The experience gained from our material confirms this opinion as 60 per cent of the abnormalities found were conduction defects. (Table 1.) The determination of the frequency of delayed A-V conduction in any series depends, in part, on

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the criteria demanded for this diagnosis. Ashman and Hull¹⁶ have noted the reciprocal relationship of the cardiac rate and the normal P-R interval and have indicated that in the presence of tachycardia the upper limits of normal A-V conduction may be less

TABLE 1

ECG ABNORMALITIES IN RHEUMATIC FEVER

Total cases of rheumatic fever	700
Total cases with abnormalities in the ECG	147 (21%)
Of the 147 cases:	
1. Conduction defects	88 (60%)
Partial A-V block	83
Complete A-V block	3
Intraventricular block	2
2. T wave changes	52 (35%)
Inversion T _{1,2} or T ₄	17
Diphasic T ₁ and T ₄	11
Flat T ₁ and T ₄	24
3. Abnormal rhythms	14 (10%)
Shifting auricular pacemaker	7
Nodal rhythm	4
Nodal escape	2
Auricular fibrillation	1
4. Miscellaneous	12 (8%)
Marked LAD or RAD	7
Inversion P ₂ and P ₃	5

TABLE II

DURATION OF A-V BLOCK IN RHEUMATIC FEVER

Of 76 cases:	Per
Days	No. Cent
0-4	11 (15)
5-8	3 (4)
9-14	39 (51)
15-21	14 (18)
22-28	6 (8)
over 3 months	3 (4)

than 0.20 second. They have also shown that in children the upper limits of normal A-V conduction are usually less than 0.20 second. These statements, however, have not received universal acceptance and no patient in our series was considered to have a prolonged P-R interval unless it exceeded 0.20 second. It is apparent that had the P-R interval been related to the cardiac rate in our series the percentage of patients with abnormal conduction would have been higher because of the frequent occurrence of tachycardia at the onset of rheumatic fever. In borderline records with P-R intervals of 0.20 to 0.22 second a reduction of at least 0.04 second in a clinically improved patient was considered as indicative of a partial A-V block. Table II shows that 4 per

cent of the patients who had delayed A-V conduction during the acute phases of rheumatic fever had apparently fixed conduction defects. The P-R interval remained prolonged for months after all signs of rheumatic activity had subsided even though the patient was allowed to get up and to be fully active. This fact must be considered before interpreting an isolated, prolonged P-R found in a routine electrocardiogram as indicative of acute carditis. The occasional observation of a prolonged P-R interval in normal aviators^{1,2} may be explained at times on the basis of rheumatic fever from a previous episode.

The transient nature of the abnormalities in conduction has been noted in the literature. The conflicting percentages of abnormal electrocardiograms in rheumatic fever can probably be attributed to the stage of the disease at which the tracings were made and the frequency with which they were taken in serial records. The extremely short duration of the abnormalities noted in some of our patients was quite striking from hours to a few days. (Fig. 1.) Data on the average duration of the delayed A-V conduction are summarized in Table II and cases illustrating the transient nature of the abnormalities follow:

CASE REPORTS

CASE 1. B. N. S., aged seventeen, was admitted to the hospital on April 4, 1944, with a history of minimal swelling and pain in the feet of three days' duration. The pain in the feet had progressed to such a degree of severity within forty-eight hours that he had been unable to sleep. Physical examination gave negative results except for a red throat and a temperature of 101°F. It was elicited, however, that he had had a cold and a sore throat intermittently since January, 1944, and four years previously he had had a febrile polyarthritis diagnosed as rheumatic fever.

The patient was placed in bed and 10 Gm. of salicylates daily were administered. He became afebrile and asymptomatic within forty-eight hours. An electrocardiogram on April 5th revealed a partial A-V block with a P-R of 0.28 second. A tracing taken a week later was

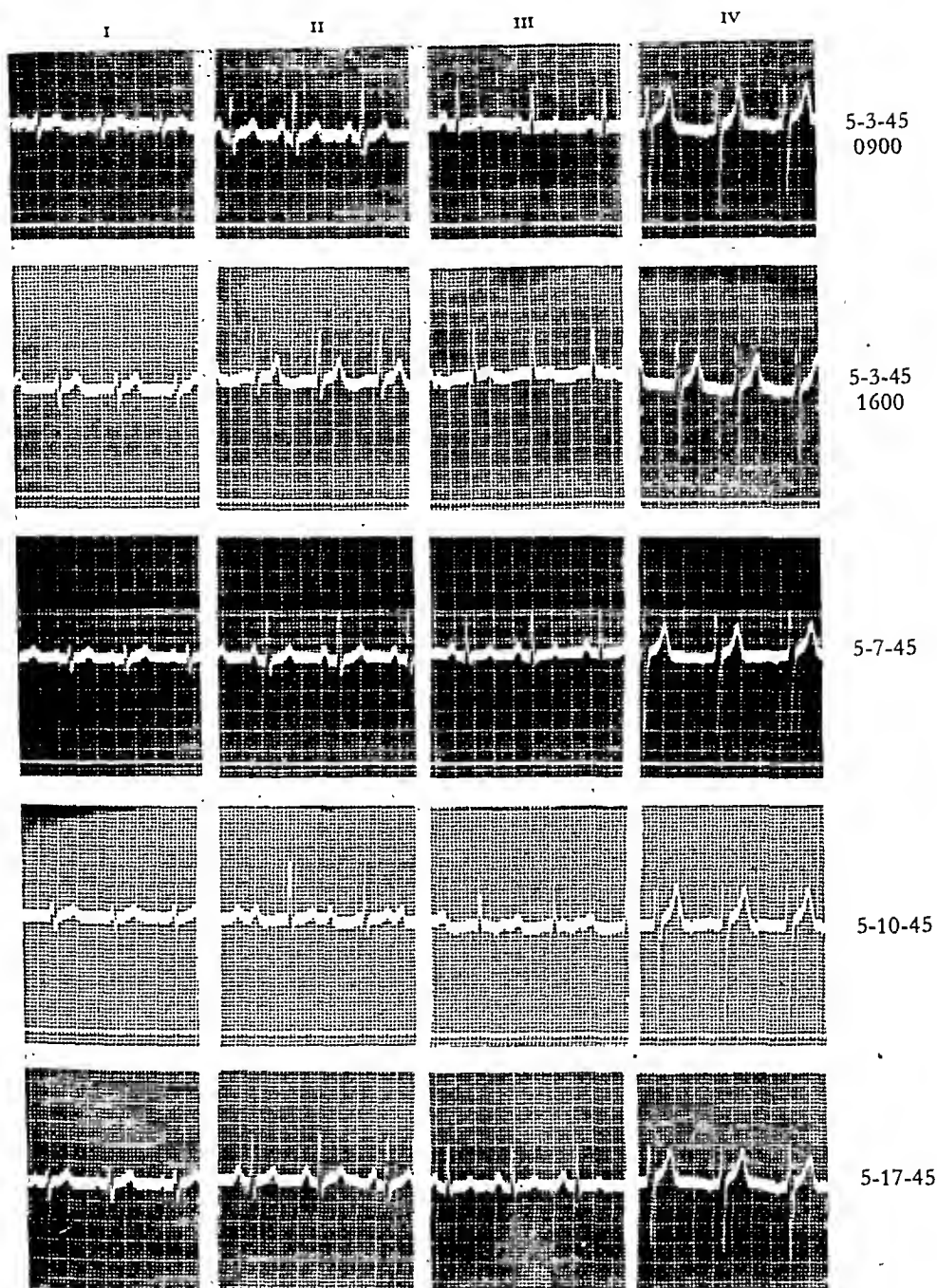


FIG. 1. Patient W. C. J., white, age nineteen. Onset of rheumatic fever occurred on February 23, 1945. Temperatures on May 3, 7, 10 and 17, 1945, were 99.2°, 98.8°, 98.6° and 99.4°F., respectively. Electrocardiogram indicates precordial pain on May 3rd as 0900 and 1600.

normal, with a P-R of 0.18 second. Clinically, the heart showed no sign of abnormality. The sedimentation rate (Westergren, the method used throughout our studies) had been 25 mm. in one hour on entry, but on serial readings gradually fell as follows: 21, 16, 15, 14, 11, 12, 10, 14, 9, to reach 6 mm. in one hour on June 12th, about two months after admission.

Comment: The electrocardiogram in this case furnished the only evidence of carditis in a patient who had no objective signs of arthritis and who complained only of pain in the feet which rapidly subsided. The initial fever had been attributed to residual pharyngitis by the admitting officer. The

electrocardiogram led to a more detailed history which revealed the previous attack of rheumatic fever. The partial A-V block was present for only one week although two months elapsed before the lowest sedimentation rate was reached.

CASE II. T. R. H., aged eighteen, was admitted to the hospital on June 11, 1943. He had recently arrived in San Francisco from an endemic rheumatic fever area in the Northwest. He complained of stiffness of his knees, ankles and elbows and stated that he had first noted the symptoms a week before. Further history revealed frequent episodes of sore throat and a weight loss of 20 pounds during his period of training as a recruit a few months before. Physical examination, including the heart, gave negative results and he was afebrile. The sedimentation rate, however, was 28 mm. in one hour and an electrocardiogram revealed a variable heart block, from partial to complete, with a P-R from 0.24 to 0.40 second. At times a nodal rhythm was present. Roentgenographic examination of the thorax gave negative results.

The patient was put to bed and salicylates were administered. By June 15, 1943, four days later, he was practically asymptomatic. No abnormal signs had appeared in the heart. The electrocardiogram was normal at this point and remained so. Serial sedimentation rates revealed figures of 28, 31, 15, 11 and on July 21st, five weeks later, it was 8 mm. in one hour.

Comment: Case II illustrates the value of the electrocardiogram as a diagnostic procedure in young adults with vague arthralgias. Rheumatic fever was suspected in this patient because he came from a highly endemic area and because he had had many episodes of soreness of the throat. Although his symptoms were minimal, the electrocardiogram indicated the presence of myocarditis. The short duration of the partial A-V block, four days only, is noteworthy.

T Wave Changes in Rheumatic Fever. Emphasis in the literature has always been placed on partial A-V block as the characteristic electrocardiographic abnormality in rheumatic fever. As stated our experience confirms this fact and the cases already reported stress the transient nature of the abnormality. We have been impressed,

however, by the relatively high incidence of T wave abnormalities in the absence of clinical pericarditis, 35 per cent of our abnormal electrocardiograms in rheumatic fever being in this category. The T wave abnormalities occur often without associ-

TABLE III
DURATION OF T WAVE CHANGES IN RHEUMATIC FEVER
Acute pericarditis excluded; flat T waves excluded;
duration noted until T₁, T₂, T₄ upright 1 mm.
Of 28 cases:

Days	
0-4.....	4
5-8.....	11
9-14.....	9
15-28.....	2
over 28.....	2

ated defects in A-V conduction, but it is not uncommon to have both delayed A-V conduction and abnormal T waves in the same tracing. Significant abnormalities of the S-T segment were infrequently seen although at times a slight elevation of this segment was observed in the limb leads which did not exceed that found normally. The appearance of T wave changes in rheumatic fever has been noted in the literature^{12-14, 17-19} but their frequency and importance as isolated findings has not been sufficiently emphasized. The types and duration of the T wave abnormalities are illustrated in Tables I and III. The inverted T waves in rheumatic fever may be short-lived, may be intermittent and variable similar to the features noted in A-V conduction and may involve Leads I, II or IV, alone or in combination. (Figs. 2 to 4.) Depending on the time the electrocardiogram is taken, changes may be seen solely in one lead (Fig. 2, 5/11) whereas at an earlier or later date other leads may be abnormal. (Fig. 2, 5/10 and 5/19.) Special care must be used to see that the precordial electrode is placed over the cardiac apex before interpreting the electrocardiogram as abnormal on the basis solely of an inverted T₄. Multiple precordial leads should be taken if doubt exists as to the position of the apical electrode. At times T₁ may be low and borderline, (Fig. 3, 4/30) but serial changes subsequently may reveal T₁

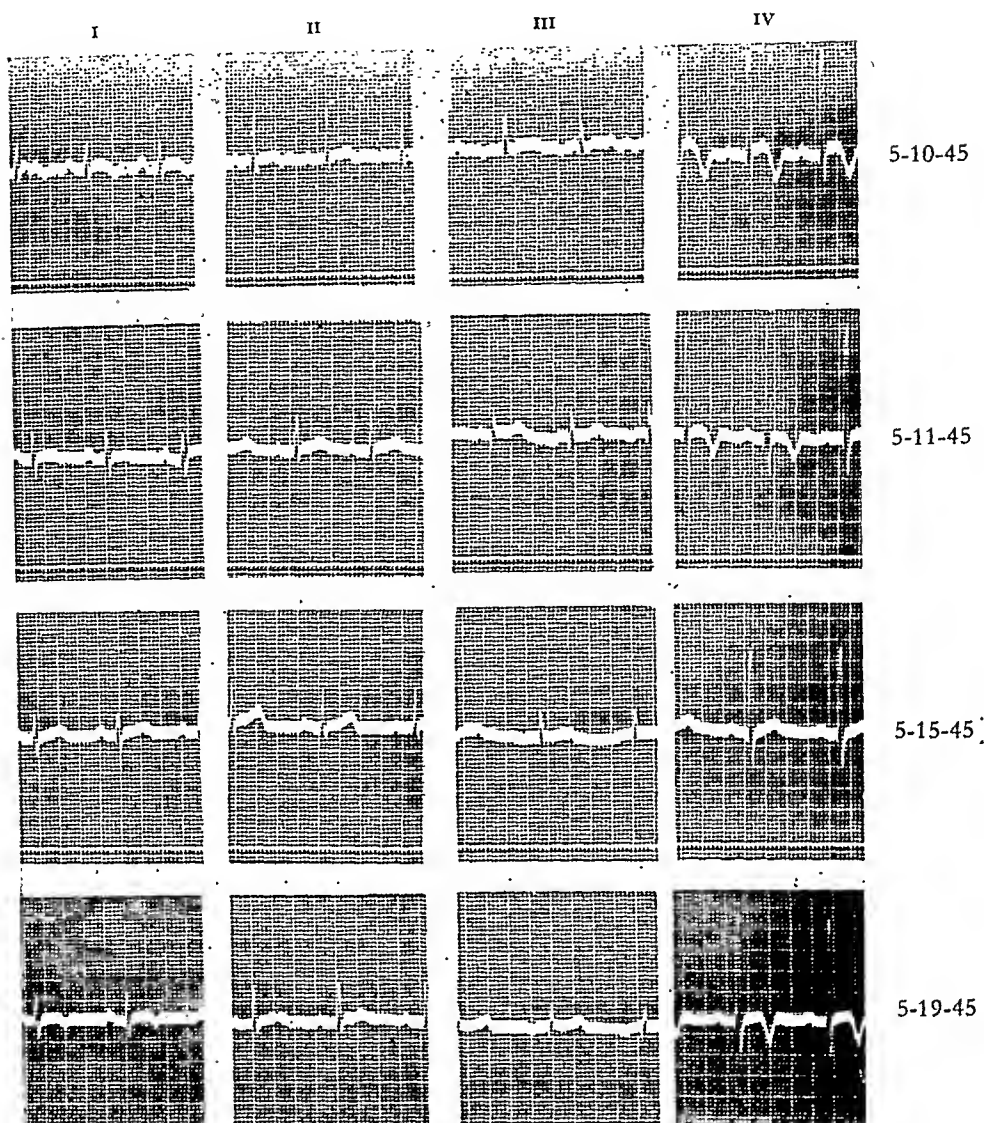


FIG. 2. Electrocardiograms of R. J. N., Case III.

to be taller (5/17), indicating that the low T_1 seen earlier was significant. These considerations emphasize the importance of serial electrocardiograms in rheumatic fever. If the patient whose records are shown in Figure 2 had had a single tracing on 5/15, the record would have been interpreted as normal yet on 5/11 and 5/19 the electrocardiogram clearly showed abnormal findings.

CASE III. R. J. N., aged twenty-eight, had been placed on the sick list on his ship on April 4, 1945, complaining of painful, swollen joints of a week's duration. His knees were involved first and over a three-day period his symptoms progressed from soreness and pain on motion to swelling and inability to walk. On the day

before he reported to the sick bay migratory polyarthritis of the ankles, elbows, wrists and feet appeared. He had had no previous rheumatic episodes but had had a sore throat ten days prior to onset of his articular symptoms. Examination on April 4th revealed swollen, red, painful metacarpophalangeal joints, and tenderness and stiffness of the elbows and knees without swelling. The heart was normal. The temperature was 101.4°F ., pulse 96 and blood pressure 124/78. The erythrocyte count was 4,100,000 and the leukocyte count 17,850 per cu. mm. of blood. The sedimentation rate was 28 mm. in one hour. The electrocardiogram at that time revealed a normal P-R interval but there was inversion of T_1 and T_2 with a flat T_3 . Roentgenographic examination of the thorax gave negative results. The patient had no precordial

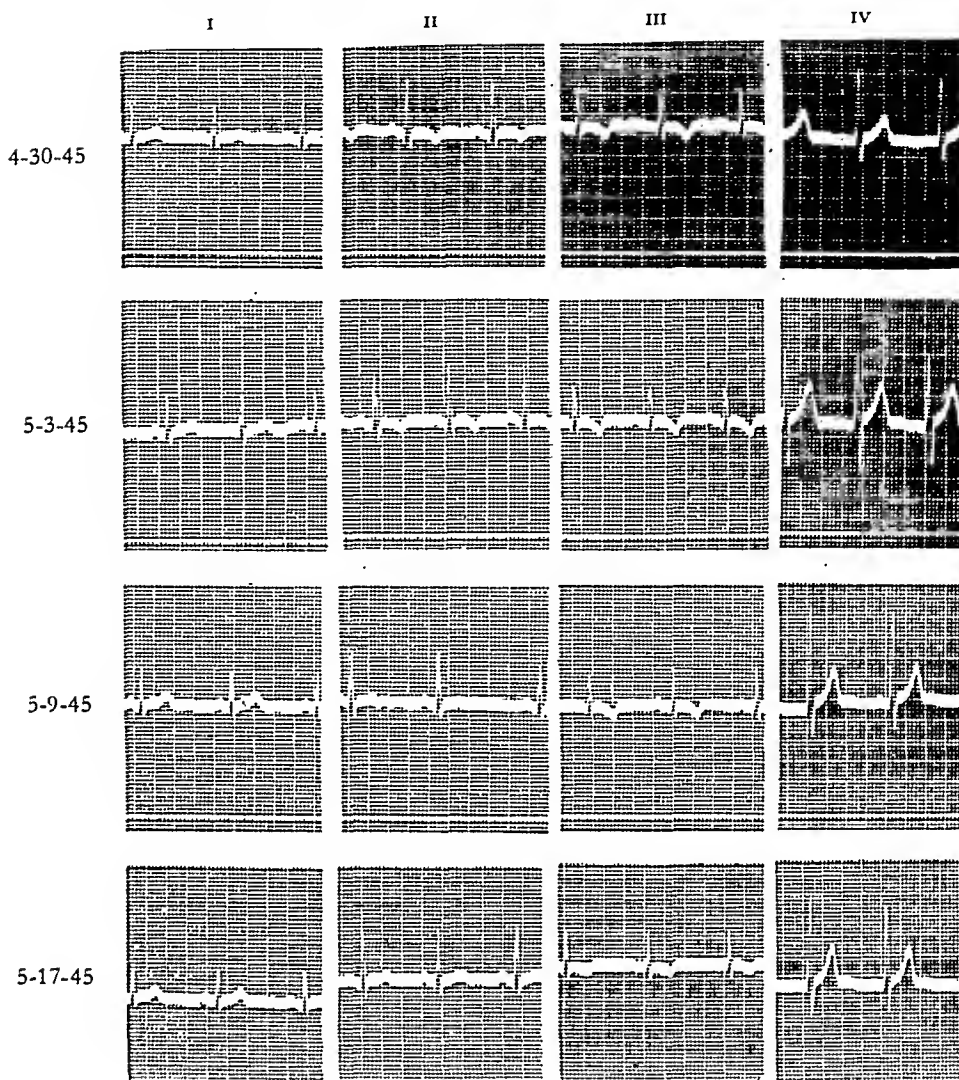


FIG. 3. Electrocardiograms of R. J. N., Case III.

pain, dyspnea or cough and the heart was normal on repeated physical examinations.

On arrival at the hospital on April 25, 1945, the patient made no complaints and physical examination showed no abnormalities. In view of his history he was put on routine rheumatic fever care. The leukocyte count at this time was 10,000 per cu. mm. of blood and the sedimentation rate 23 mm. in one hour. The electrocardiogram revealed a low T_1 , inverted T_2 and T_3 and a normal upright T_4 . The A-V conduction tracings were made and the changes in the T waves are seen in Figure 3. On May 3rd, T_1 was slightly taller but T_2 remained inverted. By May 9th, T_2 was low diphase and T_1 and T_4 were normal. On May 11th, T_2 was normally upright and the sedimentation rate had fallen to 8 mm. in one hour.

Comment: Case III illustrates a type of T wave abnormality commonly seen. T_2 is often the last to become normal. In this patient one month elapsed before the electrocardiogram was normal. At no time were there precordial pain, signs or symptoms of pericarditis and the heart was not enlarged. Partial heart block did not occur.

CASE IV. J. M. G., aged seventeen, while on a troop train en route to San Francisco, awoke with a painful right elbow without swelling or redness. On the following day the elbow was improved but the patient had pain in the lower region of his back. Four days after the initial attack he noted swelling and redness of the left ankle and the next day his right ankle became red and swollen and the left knee was painful although not swollen. He had felt perfectly well

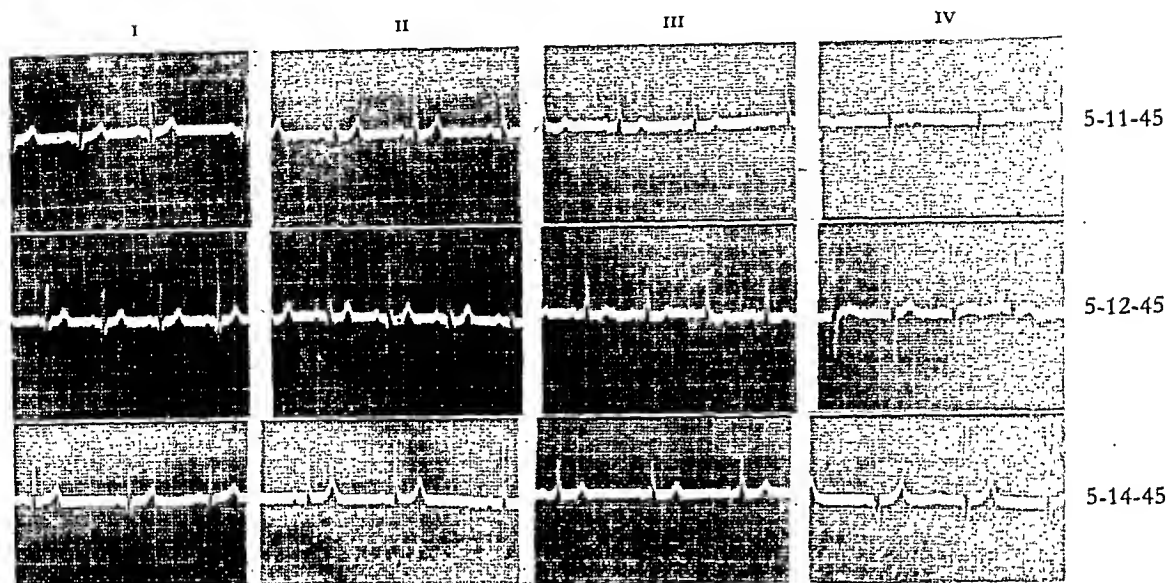


FIG. 4. Electrocardiograms of J. M. G., Case IV.

prior to this episode and had had no previous rheumatic history and no upper respiratory infection had preceded the present episode.

On arrival at the hospital on May 11th, he complained of dyspnea and fatigue on walking, pain and swelling in both ankles and pain in the left knee. A physical examination confirmed the presence of arthritis, with redness, swelling, tenderness and pain on motion of the ankles. The temperature was 100°F. The heart was not enlarged; but there was a grade 2 apical blowing systolic murmur. The urine was normal and the blood Kahn reaction was negative. There was no anemia. The leukocyte count was 12,000 per cu. mm. of blood and the sedimentation rate was 23 mm. in one hour. The electrocardiogram revealed an inverted T₄.

The patient was put to bed and given the usual dose of 10 Gm. of sodium salicylate daily. The joints improved with striking rapidity and there were neither subjective nor objective manifestations of arthritis within forty-eight to seventy-two hours. He was afebrile in thirty-six hours. The sedimentation rate fell rapidly, being 23 mm. on May 14th and 16 and 7 mm. in one hour on May 21st. The electrocardiogram showed a sequential change in T₄. This T wave became diphasic in twenty-four and normally upright in forty-eight hours. (Fig. 4.)

Comment: Case IV shows that abnormalities in T₄ may be the only deviation from normal in the electrocardiographic tracing and that these changes may be transient, just as was shown for the partial heart block.

This patient had complete symptomatic, febrile and electrocardiographic subsidence to normal within forty-eight to seventy-two hours of hospitalization. The sedimentation rate became normal in ten days. The entire episode was the shortest observed in a definitive attack of rheumatic fever.

Miscellaneous Abnormalities in Rheumatic Fever. Table I shows that abnormalities not associated with conduction defects or T wave changes were present in 18 per cent of patients with abnormal electrocardiograms. Such changes, however, rarely are present as isolated findings and when occurring alone are not considered indicative of carditis although they direct attention to the heart. When the electrocardiographic changes parallel clinical rheumatic activity and disappear with clinical recovery, one probably is justified in assuming that they represent active myocarditis. Extrasystoles were occasionally noted in our patients but were not included in the table because of the frequency with which transient premature beats occur normally. Ectopic beats with relatively rapid cardiac rates have on occasion suggested the possibility of rheumatic fever, especially when they occur in young individuals in the weeks following an infection due to hemolytic streptococcus. Master and Jaffe²⁰ found premature contractions of the heart in

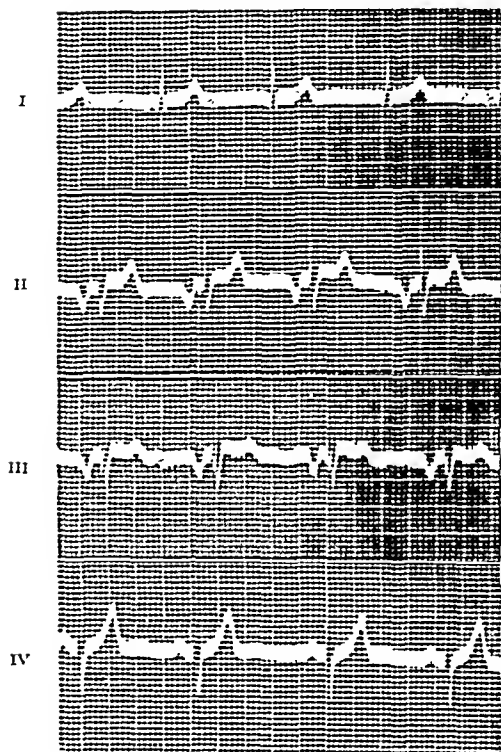


FIG. 5. Electrocardiograms of R. C. A., age twenty-one, who had rheumatic fever.

15 per cent of sixty-three patients with rheumatic fever. These authors observed auricular fibrillation in 3.2 per cent of their patients. This is in contrast to the rarity with which this arrhythmia was found in our patients and in the series of Parkinson et al.⁸ The P wave changes²⁸ (Fig. 5) may be associated with the auricular lesions described by MacCollum.²¹ Filberbaum et al.¹⁵ have also noted that significant P wave abnormalities, especially when serial changes occur, appear to be definite evidence of rheumatic cardiac involvement.

Residual Electrocardiographic Changes as Only Sign of Rheumatic Activity. Occasionally abnormalities in the electrocardiogram persist as the only signs of rheumatic activity after all other signs and symptoms have disappeared and the sedimentation rate has become normal. The question then arises as to whether such abnormalities are fixed and irreversible or whether myocarditis persists and appropriate treatment is still required. If the patient is seen for the first time at this stage with an abnormal electrocardiogram, the problem of interpretation

becomes even more difficult. It has been our experience that irreversible delayed A-V conduction persists in approximately 4 per cent of patients with rheumatic fever who had a partial A-V block during the acute phase while persistence of T wave abnormalities is less common. Nevertheless, when a patient with rheumatic fever is kept under observation in whom the electrocardiographic abnormalities have not disappeared, the residual abnormalities should be considered as indicative of rheumatic activity until proved otherwise. The patients whose cases are to be reported in the following were placed on continued rest in bed for a reasonable period after the subsidence of all signs of activity except those of an abnormal electrocardiogram. These patients were then allowed to get up cautiously and both had evidences of mild recrudescence, indicating that even though the electrocardiographic abnormalities were isolated signs of activity they were significant. In other cases, however, recrudescence did not occur even after full physical activity was allowed; electrocardiographic abnormalities persisted as the sole objective vestige of the previous rheumatic fever.

CASE V. S. G. M., aged twenty-two, was admitted to the hospital on March 6, 1945. He had had a previous attack of rheumatic fever in 1939, lasting one month. His present episode began on February 13, 1945, without antecedent upper respiratory or other infection of which he was aware. A migratory polyarthritis of the left knee, shoulders, left wrist and hands developed, the joints being involved in succession a few days apart and each becoming improved in three to four days. On February 26th, he noticed dyspnea on walking and there was some aching abdominal pain with mild diarrhea. He reported to his local sick bay at which examination revealed a temperature of 101.6°F., pulse of 116 and respiration of 24. His blood pressure was 125/75. The heart was not enlarged but there was a long, blowing apical systolic murmur, grade 2, and the pulmonary second sound was greatly accentuated. No rub was audible. The involved joints were swollen, painful on motion and tender. The laboratory data revealed no anemia, a leukocyte count of 10,000

with 76 per cent polymorphonuclear cells. The sedimentation rate was 25 mm. in one hour. The electrocardiogram showed a P-R interval of 0.20 second, delayed for the tachycardia. T_1 and T_2 were low and T_4 was diphasic.

The patient was put to bed and given 30 gr. of sodium salicylate every four hours; he complained of severe tinnitus and deafness after twelve hours so the dose was reduced to 20 gr. every four hours which alleviated the toxic symptoms. He showed marked clinical improvement in seventy-two hours as far as fever and articular symptoms were concerned, but on March 3rd, a soft, early aortic diastolic murmur was heard.

On arrival at the hospital on March 6th, the patient had moderate tenderness in his knees, shoulders, elbows and left wrist but he complained only of mild aching in the joints. His temperature was 99°F., pulse 84 and respiration 20. Cardiac findings were unchanged. Urine was negative but the hemoglobin was 71 per cent and the prothrombin 75 per cent. The sedimentation rate was 19 mm. in one hour. The electrocardiogram showed a P-R of 0.24 second; T_1 , T_2 and T_4 were inverted. He was placed on rest in bed and salicylates and within seventy-two hours the aching in the joints had subsided. He remained afebrile. The aortic diastolic murmur disappeared and the apical systolic murmur decreased in intensity. The sedimentation rate gradually fell to a normal level of 10 mm. in one hour on April 11, and 5 mm. in one hour by April 17, 1945, forty-two days after entry. The P-R interval had increased to 0.40 second on March 14th, was 0.33 second on March 19th, and again on March 22nd, but by April 6th, it was 0.20 second with a cardiac rate of 73. The T waves were still abnormal on this date but had changed from inverted to low diphasic in leads I and IV. By April 23rd, he was afebrile, asymptomatic and the sedimentation rate had been normal for two weeks. The P-R interval was 0.20 second but T_1 was still flat and T_4 slightly inverted. The patient was anxious to get up and the question arose as to the significance of the residual T changes since they were the only signs of activity. It was decided to allow him to get up and about the ward for an hour, twice daily, and to observe the results. Within a week T_1 , T_2 and T_4 had again become inverted; after two weeks the P-R interval had increased to 0.40 second. He had no symptoms or rise in temperature despite the

increase in electrocardiographic abnormalities. The sedimentation rate increased from 3 mm. in one hour on April 23rd, to 13 mm. in one hour on May 10, 1945. He was returned to complete rest in bed and by May 20th, the T waves were low to flat. The patient was then transferred to a convalescent hospital.

Comment: Case v illustrates that residual T wave abnormalities, even though not marked, may represent the only objective evidence of continued rheumatic activity. Interpretation is facilitated when a single physician follows the course of the disease, but it may be very difficult if the patient is seen at a late stage without the benefit of previous electrocardiographic studies. If this patient had first been observed on April 23, 1945, the significance of the flat T waves would have been difficult to evaluate. Careful observation when a patient is first allowed to get up will aid in evaluating the significance of residual electrocardiographic abnormalities. This case emphasizes the importance of the advice of Barnes²² that a patient should be kept in bed until all signs of activity have disappeared; residual electrocardiographic changes as isolated findings must be considered as such signs. Only continued observation will allow one to conclude that residual electrocardiographic changes are fixed and not necessarily associated with rheumatic activity.

CASE VI. G. A. Z., aged thirty-one, was admitted to the hospital on December 3, 1944. He had been overseas for twenty-two months when in mid-October of 1944 migratory polyarthritis developed and he complained of fever, fatigue and hiccups. He was treated with rest in bed and salicylates. One month before his transfer he began to have palpitations and for three days prior to entry he had continued to ache in the region of his precordium. Administration of salicylates had been discontinued for one month.

On arrival he complained of aching in the precordium, palpitations, fatigue and aching pain in the wrists, knees and ankles. Examination gave negative results except for slight pain on full range of motion of the affected joints. The temperature was 99.6°F., pulse 105 and

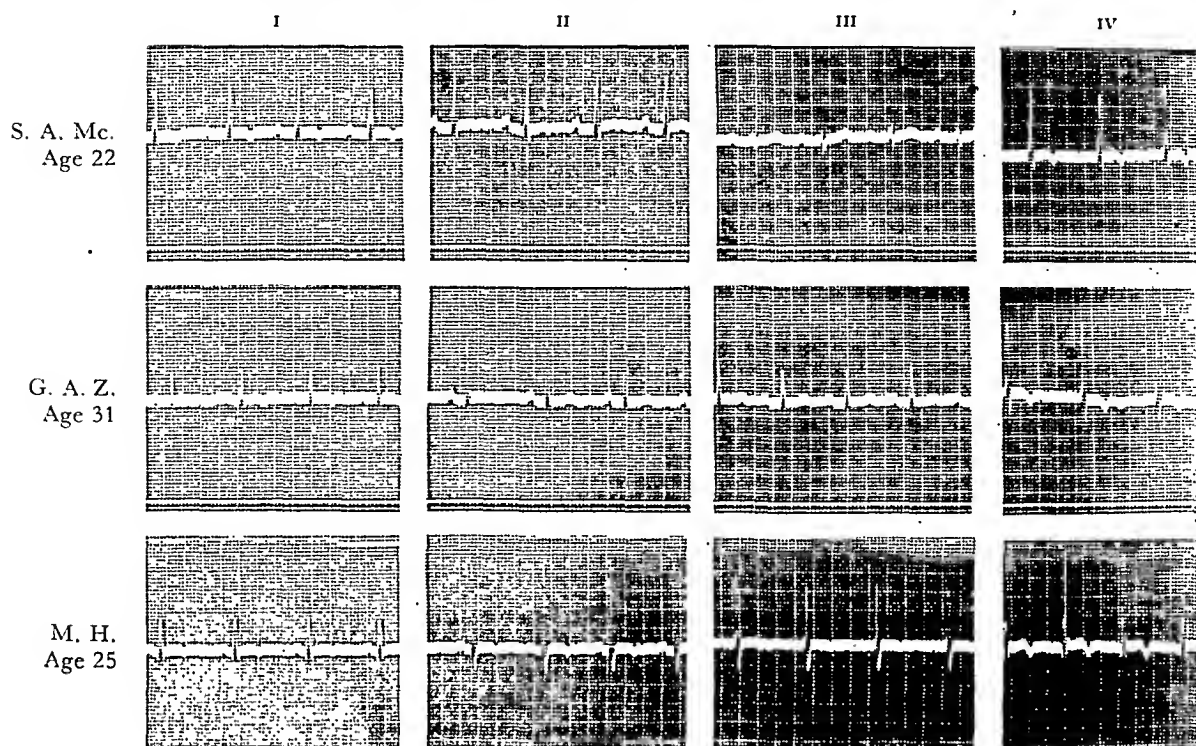


FIG. 6. Electrocardiograms showing T changes in rheumatic fever in three patients.

respiration 20. Laboratory data revealed a normal urine, normal hemoglobin and erythrocyte count, a leukocyte count of 10,000, sedimentation rate of 7 mm. in one hour and a negative blood Kahn reaction. Roentgenologic examination of the thorax was negative; the heart was not enlarged. The electrocardiogram showed the P-R to be delayed, being 0.21 second with a cardiac rate of 101. T_1 and T_4 were inverted, T_2 was flat. (Fig. 6.)

The patient was put to bed and given full doses of salicylates. The sedimentation rates were normal on repeated tests, he was afebrile within three days and by January 9, 1945, he had no pain in the joint or the precordium. By January 15th, the P-R was normal, being 0.19 second, with a cardiac rate of 75 while T_1 was flat to low upright and T_4 small and slightly inverted. He was then transferred to a convalescent hospital.

Comment: Case VI illustrates again that abnormalities in the electrocardiogram may be the major objective evidences of residual rheumatic activity. In this patient salicylate therapy had been discontinued; he complained of fatigue, palpitations, painful joints and aching in the precordial region and had a temperature of 99.6°F. for three

days. The sedimentation rate was normal when checked twice a week during the six weeks of observation. The electrocardiogram revealed abnormal T waves and delayed A-V conduction. The symptoms and low fever subsided with salicylate therapy, the A-V conduction became normal but six weeks later the T waves had not yet become normal. Although active carditis was present in this patient as well as the one discussed in Case V, the sedimentation rate was normal at the time in each instance. This is of special interest since, as a general rule, the sedimentation rate is the last sign to become normal.

Negative Electrocardiograms in the Presence of Clinical Myocarditis and Endocarditis. It is important to indicate limitations of the electrocardiogram and to emphasize the fact that this test does not replace, but is an adjunct to, careful clinical study. In some patients with rheumatic fever definite carditis as manifested by cardiac enlargement or significant diastolic murmurs may appear without diagnostic electrocardiographic changes. Repeated examination of the heart is therefore essential in managing a

patient with rheumatic fever to determine the presence of carditis. This is particularly true since diastolic murmurs may not be present at the onset of rheumatic fever and may not appear for several weeks after the acute febrile and articular manifestations have subsided (Case v) and the patient apparently is progressing satisfactorily.

CASE VII. J. F. E., aged twenty-five, was admitted to the hospital on April 3, 1945, with a diagnosis of acute arthritis. He had had a sore throat on several occasions in the past two years, the last time on February 15, 1945. On March 10th, he had an aching pain in the right knee but without swelling. He continued ambulant but a week later the pain was so severe he could not stand and swelling had appeared in the knee. He reported to his sick bay at which time it was noted that his right knee was swollen, red, hot and tender. The sedimentation rate was 25 mm. in one hour and the temperature 100.2°F. The patient was put to bed with hot packs and given 3 Gm. of salicylates daily. He was afebrile in five days and the symptoms present in the knee subsided in a week. The sedimentation rate was 10 mm. in one hour on March 26th. No electrocardiogram was taken. The patient was returned to duty on March 29th. Within forty-eight hours, pain and swelling in the right knee had reappeared and the left knee was similarly affected the next day. The patient was then transferred to us.

On arrival he had a temperature of 100°F. and slight swelling and tenderness of both knees. The heart was normal. Laboratory data revealed moderate anemia. The sedimentation rate was 25 mm. in one hour and the electrocardiogram was normal.

The patient was placed on salicylates, 10 Gm. daily, and put to bed. He was afebrile within twenty-four hours and the joints were normal within a week. Serial electrocardiograms, taken twice weekly for two months, remained normal. The sedimentation rate fell gradually, serial determinations twice a week being 18, 15, 13, 11, 12, 10, 14, 13 and finally 5 mm. in one hour on May 21st, seven weeks after entry.

On May 22nd when the sedimentation rate was 5 mm. in one hour and the patient was afebrile, subcutaneous nodules about the knees were noted. On full range of motion the knees were slightly painful. The patient was still on salicylates. He felt "washed out" and was easily

fatigued upon the slightest exertion. At this period an early aortic diastolic murmur was noted which persisted until the patient was transferred to a convalescent hospital. The sedimentation rate remained normal to the last, being 5 and 6 mm. in one hour on subsequent determinations.

Comment: Case VII illustrates: (1) initial monarticular involvement, (2) rapidity of recurrence with premature physical activity, (3) the need for clinical as well as electrocardiographic study since serial tracings were normal and yet a diastolic murmur appeared and (4) the presence of rheumatic activity despite a normal sedimentation rate. The diagnosis of rheumatic fever was not made during the initial attack of arthritis in this patient, presumably because of the rapid response to rest and small doses of salicylates.

CASE VIII. F. W. T., aged twenty-six, became ill with scarlet fever on February 21, 1945. He recovered promptly and was apparently well until March 17th, when he complained of aching pain in the ankles and feet of four days' duration which became so severe that he could not stand or walk. In the succeeding ten days his fingers, wrists, knees and shoulders became involved and he was transferred to the hospital on March 27, 1945. Examination revealed a temperature of 100.4°F., slightly enlarged tonsils, subcutaneous nodules over the tendons of the fingertips and an erythematous rash over the flexor surface of the right arm. The ankles and soles were tender and swollen and the skin over the feet showed typical postscarlatinal desquamation. The heart was normal; the urine showed a trace of albumin; the sedimentation rate was 26 mm. in one hour. The blood count showed a hemoglobin of 11 Gm.; the leukocyte count was 15,400; the electrocardiogram was normal.

The patient rapidly improved on routine rheumatic fever therapy but continued to complain of fatigue. An electrocardiogram was taken twice weekly and remained negative throughout his course in the hospital. On April 30th, when the patient was afebrile and the joints were normal, a soft, early diastolic murmur was noted. The murmur was consistently present from then on until the patient was transferred to a convalescent hospital on May

8th. The sedimentation rate remained elevated, being 20 mm. in one hour at the time of transfer.

Comment: Cases VII and VIII emphasize the necessity for constant vigilance and searching for significant murmurs even though the electrocardiogram remains normal. It is noteworthy that the aortic diastolic murmur appeared relatively late in the course of the disease when the acute febrile and arthritic phase had subsided.

COMMENTS

It is clear from the cases presented here that the electrocardiogram reveals unequivocal evidence of carditis in some cases of rheumatic fever in which the diagnosis would otherwise be in doubt. Partial heart block and inversion of the T waves in leads other than III are of diagnostic significance when they occur in an illness compatible with rheumatic fever. This is especially true if the improvement in the electrocardiogram parallels the clinical progress of the patient. The appearance of typical electrocardiographic patterns has clarified the nature of many mild cases of illness following streptococcal infections, revealing that they represent changes due to rheumatic fever. The transient nature of the abnormalities makes it necessary to obtain electrocardiographic tracings as early as possible and to repeat them frequently in the course of the disease.

The late appearance of transient abnormalities in the electrocardiogram when the patient seems to be progressing well is valuable in pointing out subclinical recrudescence characteristic of polycyclic rheumatic fever. These changes may occur while the patient is still in bed on salicylate therapy and without the patient being aware of the recrudescence activity.

Control of the process of ambulation during convalescence by use of frequent electrocardiograms is very important. Evidence of reactivation may be first or even solely manifested by the characteristic partial A-V block, inverted T waves, or both and may be entirely subclinical. It is important to recognize this reactivation so

as to take the necessary therapeutic measures to minimize damage to the heart.

Diagnosis of rheumatic fever is not warranted when electrocardiographic changes, such as described, appear as isolated findings in a routine electrocardiogram in the absence of symptoms compatible with rheumatic fever. The range of normal variations in the electrocardiogram is great; some patients may have had previous myocarditis and unless the abnormalities disappear in a short time parallel with the clinical symptoms, diagnosis of rheumatic fever cannot be made. Abnormalities in the electrocardiogram which do not disappear with treatment or which may be a normal variant cannot be used as evidence of active carditis, except in those patients with obvious clinical rheumatic fever with carditis in whom the electrocardiographic abnormalities remain fixed and do not revert to normal as the rheumatic activity subsides.

It must be re-emphasized that although the electrocardiogram reveals carditis in young adults with rheumatic fever more than twice as often as all other criteria of carditis combined, some patients will demonstrate clinical evidence of carditis such as diastolic murmurs and cardiac enlargement in the absence of electrocardiographic abnormalities. Therefore, clinical study must be maintained as reliance solely on the electrocardiogram will inevitably lead to errors.

The mechanism of the T wave changes occurring in rheumatic fever is obscure. Symptoms or signs of acute pericarditis are always carefully sought for when inversion of the T wave occurs in all leads even without the preliminary stage of elevated S-T segments. Despite frequent examinations the majority of patients with inverted T waves did not have a pericardial friction rub or enlargement of the cardiac shadow. Subclinical pericarditis cannot be excluded, however, because of the known discrepancy in clinical and autopsy incidence of this finding in rheumatic fever. Bland and Jones²³ found pericarditis present clinically

in 35 per cent of fatal cases of rheumatic fever with some evidence of pericarditis in 80 per cent at autopsy. Electrocardiographic tracings of patients with rheumatic fever without clinical pericarditis are often indistinguishable from tracings of patients with obvious pericarditis. Undoubtedly subclinical pericarditis is responsible for many of the T wave abnormalities previously described.

Involvement of the coronary arteries in rheumatic fever has been frequently noted at autopsy.²⁴⁻²⁶ Karsner and Bayless²⁴ stated that rheumatic fever produces disease of the coronary arteries regularly, with inflammatory or fibrotic lesions. It is possible, therefore, that the T wave changes in rheumatic fever may be the result of coronary arteritis. However, the lack of reciprocal changes in T₁ and T₃ and of S-T and T, so characteristic of arteriosclerotic coronary disease, is against this assumption. Evolutionary changes typical of acute coronary disease,²⁷ with gradual waxing and waning of the T waves, is almost never seen in rheumatic fever. Anginal pain is rare in rheumatic fever although precordial pain is common, and it is probable that the coronary arteritis of rheumatic fever, as observed on histologic studies, is rarely of clinical significance.

Myocarditis, *per se*, undoubtedly is important in the production of T wave changes and probably shares with subclinical pericarditis the basis of these abnormal electrocardiographic findings. Since subepicardial myocarditis is thought to be responsible for the electrocardiographic changes seen in pericarditis, the common denominator is myocarditis.

SUMMARY

1. The most frequent criterion of carditis in rheumatic fever in young adults is represented by abnormalities in the electrocardiogram. Cardiac enlargement, pericarditis, cardiac failure, diastolic murmurs and unequivocally significant systolic murmurs are relatively infrequent in this group of patients.

2. The most common abnormality in the electrocardiogram in rheumatic fever is a partial A-V block. This is present in 60 per cent of those patients who show electrocardiographic abnormalities.

3. Inversion of T₁, T₂ or T₄, alone or in combination, represents the second most frequent abnormality being found in 35 per cent of those patients in whom electrocardiographic abnormalities are present. Serial records are of value in determining the significance of borderline T changes.

4. Abnormalities in the electrocardiogram other than conduction defects, ST-T wave changes and major arrhythmias occur in rheumatic fever; however, great care must be exercised before interpreting them as indicative of active carditis when they are present as the only abnormal electrocardiographic finding in a single tracing. Significant serial changes may allow one to interpret these minor abnormalities as evidence of cardiac involvement.

5. Significant abnormalities in the electrocardiogram are a major manifestation of rheumatic fever and are of value in recognizing atypical cases.

6. The electrocardiogram may reveal the polycyclic nature of the course of a patient with rheumatic fever in the absence of clinical evidence of such polycyclic activity. This indicates the necessity of taking electrocardiograms early and frequently during the course of the disease.

7. Abnormalities in the electrocardiogram may indicate reactivation of the rheumatic process during convalescence when the patient is first allowed some physical activity. This may occur in association with a secondary rise in fever, elevation of the sedimentation rate or as an isolated finding. The carditis thus revealed may be subclinical and demands appropriate therapy. The process of ambulation requires electrocardiographic observations to determine the presence of renewed activity.

8. Carditis may be obvious clinically in the absence of abnormalities in the electrocardiogram despite early and frequent tracings.

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Oxygen Therapy in Acute Rheumatic Carditis in Children*

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THE physiologic basis for the therapeutic use of oxygen in heart disease lies in the fact that the oxygen tension of the arterial blood may be critically diminished in patients suffering from cardiac disease. Anoxemia of the heart muscle means that the cells of the myocardium receive their supply of oxygen at an abnormally low pressure. The basal consumption of oxygen is not measurably altered. The ill effects are due primarily to the low pressure of free oxygen in the blood to which the cells of the heart muscle are exposed, resulting in a disturbance in cell metabolism. Inhalation of an oxygen-enriched atmosphere containing 40 to 60 per cent oxygen raises the oxygen saturation of the arterial blood to normal in such patients, restoring the oxygen tension and presumably reversing the ill effects of anoxemia. These physiologic principles of oxygen therapy have been adequately summarized by Haldane,¹ Lundsgaard and Van Slyke,² Barcroft,³ Meakins and Davies⁴ and Peters and Van Slyke.⁵

Use of oxygen as a therapeutic agent in heart disease has been assiduously explored both in England and in this country for the past twenty-five years. Barach⁶ and his associates have studied the effect of oxygen therapy in various types of heart disease and have concluded that in congestive heart failure and in acute coronary thrombosis oxygen very often is a life-saving measure. They were impressed with the fact, however, that successes with this form of therapy were obtained more frequently in the degenerative type of heart disease

than in the acute inflammatory type of heart disease such as rheumatic carditis. It is implied from their observations that oxygen therapy is of little value in the treatment of congestive heart failure due to rheumatic heart disease since cardiac failure here is a manifestation of rheumatic activity which may not be altered by oxygen therapy. On the other hand, Poulton⁷ has demonstrated that patients suffering from rheumatic carditis with or without failure showed marked clinical improvement when treated in a 50 per cent oxygen atmosphere; there was a rapid fall in temperature and pulse rate, alteration of murmurs, diminution in the size of the heart and significant electrocardiographic changes. He found that the incidence of valvular heart disease was far lower in his treated patients than in the control group of patients. Two years of experience with oxygen therapy in rheumatic carditis in children at the St. Francis Sanatorium confirms the observations of Poulton in the main but also suggests a possible explanation for the failures reported by Barach.

It is the purpose of this paper to present a preliminary report on the effect of oxygen therapy on rheumatic carditis in children. The observations will be limited to a discussion of the effect of long residence in a high oxygen atmosphere upon the clinical course of rheumatic carditis with and without cardiac failure. The mechanisms by which these clinical effects are attained, form the basis for further investigation and will be reported in subsequent papers.

* From the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, N. Y. This study was made possible through a grant given by The Linde Air Products Company, New York, N. Y.

METHOD OF ADMINISTRATION OF OXYGEN

Methods of administration of oxygen have undergone many changes in the past quarter of a century. These methods are fully described by Barach.⁸ The aim has been to develop a method by which adequate and well controlled

which are kept in a special room on the laboratory floor. Oxygen pressure in the tanks and the amount of oxygen delivered to each room are carefully controlled. The temperature of the room is kept at a level of 66 to 68°F. by means of rheostats controlling the activity of compressors.

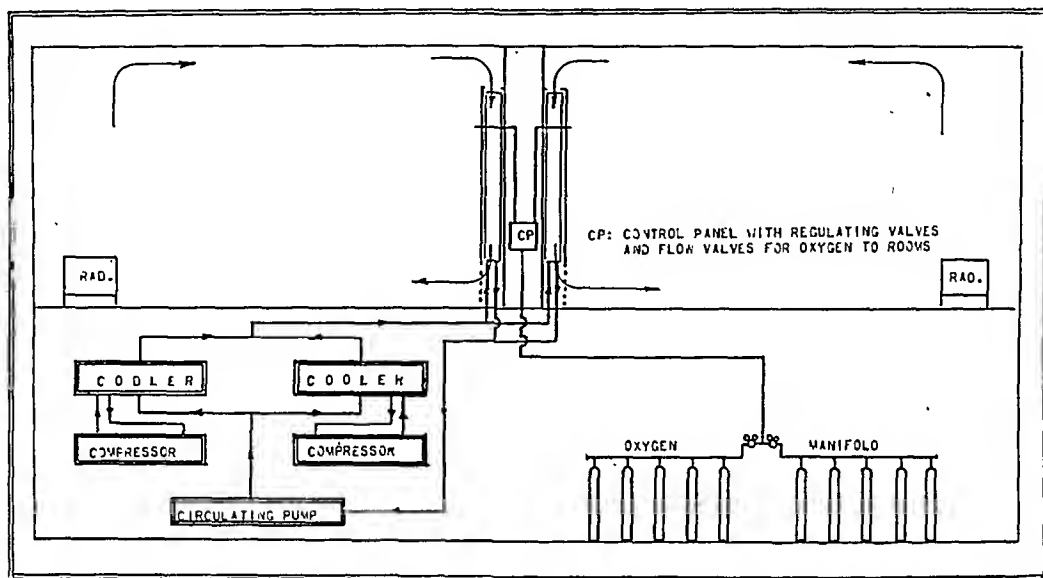


FIG. 1. A schematic diagram of the oxygen chambers showing the air-conditioning unit and also the source of oxygen.

concentrations of oxygen could be administered to the patient with a minimum of physical and emotional discomfort. Many attempts have been made to build oxygen chambers which would meet these requirements. In England, oxygen chambers were constructed by Barcroft, Hunt and Dufton⁹ mainly for physiologic investigation on the deleterious effects of low concentration of oxygen. Similar chambers were used by Campbell and Poulton.¹⁰ In this country, interest was stimulated by the construction of an oxygen chamber at the Rockefeller Institute by Stadie¹¹ in 1922. At the Mayo Foundation oxygen chambers were constructed in 1926.¹² Barach more recently devised a relatively inexpensive oxygen chamber at the Presbyterian Hospital in New York.¹³

At the Saint Francis Sanatorium two chambers were completed in 1944. These were modeled after the oxygen chamber developed by Barach. By use of pipes containing circulating ice water on one side of the room and a steam radiator on the other (Fig. 1), cooling and drying of the atmosphere, and air movement, is accomplished without the use of noisy motors. Oxygen is delivered from a battery of tanks

The delivery of oxygen is controlled by flow meters and the concentration of oxygen in the rooms is measured by instruments installed for that purpose. The latter two instruments are within view of the nurse in charge of the rooms. Provisions have been made for sampling of air through a series of tubings leading from the oxygen room to the laboratory floor.

In long-continued oxygen therapy the primary consideration in choosing the method of administration is the comfort of the patient. This is particularly true in the use of oxygen therapy for children. The mask, nasal catheter and tent are poorly tolerated by children. The oxygen room offers many advantages in long-continued oxygen therapy:

1. The oxygen concentration, temperature and humidity of the chambers can be controlled with a high degree of accuracy. Medical and nursing attention can be carried on with practically no variation in the concentration of oxygen. Frequent examination of patients and the carrying on of complex procedures of study and treatment are performed without any change of oxygen concentration of the rooms

and thus with a minimum of discomfort to the patient.

2. All fear implied in oxygen therapy is spared the patient. There is, in most instances, no recognition by the child of the fact that oxygen is being administered. The room does not look unlike any other hospital dormitory. Mechanical appliances and annoying motor noises are absent.

3. The clinical course of cardiac disease in an oxygen-enriched atmosphere can be observed with a minimum of emotional disturbances commonly seen as a result of other methods of oxygen administration.

4. Studies in the physiology of oxygen therapy can be made under highly controlled conditions, and with minimum fluctuations in the desired levels of oxygen concentration, temperature and humidity.

5. Finally, the expense of up-keep is, in our experience, no greater than any other form of oxygen therapy since three children are treated in one room which uses not more than four tanks of oxygen daily. Furthermore, the stability of these rooms and the simplicity of construction brings the cost of repair to a minimum.

MATERIAL AND METHOD OF STUDY

Forty-four children, seven to sixteen years of age, presenting unequivocal evidence of acute rheumatic carditis were treated in the oxygen chambers for variable periods of time. All patients in this group had clear clinical evidence of mitral disease; three of these had, in addition, evidence of aortic insufficiency and ten had aortic stenosis and insufficiency. The majority of children had moderately enlarged hearts; many had subjective evidence of cardiac insufficiency and some had obvious signs and symptoms of congestive heart failure. All patients presented both clinical and laboratory evidence of rheumatic activity;¹⁴ some were treated at the onset of the rheumatic episode, others many months after the onset; some presented "exudative" rheumatic manifestations while others had many of the "proliferative" phenomena.

Duration of residence in the oxygen chamber varied from twenty-four hours to forty weeks. Only three of the children were treated for less than one week; the average period of treatment was about twelve weeks and the majority of children received more than ten weeks of oxygen therapy. Each patient in this group was

observed for a period of not less than two weeks prior to treatment and for many weeks or months following therapy. Oxygen therapy was continued uninterruptedly day and night. None of the children was removed from the oxygen chambers during the entire period of residence except on rare occasions for roentgenographic studies. All other laboratory and clinical procedures were carried on in the chambers. Residence in oxygen was continued until there was definite evidence of success or failure of this form of therapy except when the patient demonstrated unequivocal symptoms of intolerance to high concentrations of oxygen. In most cases residence in the chamber was discontinued gradually by increasing daily the period of residence outside of the chamber.

Great care was taken in keeping the oxygen concentration constant at a level of 45 to 50 per cent. The fluctuation was at no time greater than 5 per cent day or night (two-hour recordings were kept). The temperature was kept constant at a level of 66 to 68°F. and the humidity fluctuated between 60 and 70 per cent. The barometric pressure did not differ from that recorded outside of the oxygen chambers. Carbon dioxide concentration was permitted to rise to a level of 1.3 to 1.5 per cent. During the course of this study no attempt was made to lower the carbon dioxide concentration.* Preliminary studies were made upon the bacterial content of the oxygen chambers. No significant bacterial findings were noted as to number and type.

Other forms of cardiac therapy were instituted only when urgently indicated. Salicylates were withheld except in frank polyarthritides with pain. The diet did not differ in any respect from the usual well balanced diet given to all other patients at the sanatorium. Patients received the usual nursing care and every attempt was made to avoid emotional disturbances. In most instances these patients were unaware that they were receiving oxygen therapy. Frequent and detailed observations were made to evaluate the clinical behavior of the patient, auscultatory changes in the heart, effect upon venous pressure, blood circulation time, respiration mechanism and the progress of rheumatic activity.

* Earlier observations corroborated the suggestion of Henderson and his associates^{15,16} that the inhalation of carbon dioxide above 1 per cent causes stimulation of the respiratory center and deeper respiration and thereby increases the effectiveness of oxygen inhalation.

RESULTS

Classification of Cases. Early in the course of this study it became clear that patients observed under treatment fell into three distinct groups:* (1) those who seem to react favorably to oxygen therapy, (2) those who were not benefited and (3) those who showed marked intolerance to this form of therapy. The difference in reaction to oxygen therapy in these three groups was striking. Of the forty-four children studied, three were intolerant to oxygen, seventeen did not show any improvement and twenty-four showed palpable to striking improvement under oxygen therapy. Further observation demonstrated clearly that these three groups of patients differed in important clinical respects:

1. *"Responsive" Cases:* Twenty-four of the forty-four patients showed definite improvement as a result of oxygen therapy. On admission to oxygen therapy, all of these children had auscultatory signs of valvular disease and all showed impressive evidence of acute rheumatic carditis. Some showed other exudative manifestations, polyarthritides, arthralgia, erythemas, pleuritis, etc. Symptoms of cardiac insufficiency, i.e., dyspnea, easy fatigability, etc., seemed to express the functional disturbance of the acutely inflamed heart rather than mechanical disability resulting from previous bouts of carditis. Some patients had low grade fever. The erythrocyte sedimentation rate was elevated in most of these cases and the hemoglobin was depressed. The heart was tumultuous and the cardiogram showed moderate to marked prolongation of the electrical systole.

2. *"Unresponsive" Cases:* Seventeen of the forty-four treated children were not benefited by oxygen therapy. Most of these were advanced cardiacs with a long-standing carditis and evidence of minimal or severe heart failure. Most of these children showed evidence of the proliferative phase of

rheumatic disease (nodules). The cardiac disability was of long standing. All of these children had moderate or marked hypertrophy of the heart and well established valvular defects of long duration. In addition, most of these children from time to time showed other visceral manifestations of rheumatic disease: hepatic enlargement without evidence of right heart failure; pulmonary signs: pneumonitis, pleuritis or pneumonia and occasionally gastrointestinal manifestations.

Few of these children showed the usual laboratory evidence of rheumatic activity. The hemoglobin was not depressed. The erythrocyte sedimentation rate was elevated only slightly in one-half of the patients. The white blood count was normal. The temperature was low grade or normal. On the other hand, both clinically and cardiographically, all of these children showed unequivocal evidence of carditis. The heart was unstable and tumultuous and the murmurs and sounds were ever changing.

These patients then were advanced rheumatic cardiacs showing clinical evidence of the proliferative phase of rheumatic disease, marked mechanical cardiac disability and exudative phenomena of lesser degree.

3. *Group Showing Intolerance to Oxygen Therapy:* The three children who could not tolerate oxygen therapy belonged to the "bronchitic" type of rheumatic carditis. The musical râles in the chest were constant and widespread. An allergic etiology in this group cannot be ruled out. Our experience, however, leads to the impression that this manifestation is part of the picture of rheumatic activity rather than intercurrent allergic disease. Children having rheumatic carditis and evidence of widespread bronchitis present an unfavorable prognosis as to life and degree of cardiac damage. They do not react favorably to any form of therapy during the active phase of rheumatic disease. They are intolerant to salicylates and are markedly sensitive to digitalis therapy during the phase of congestive failure.

* Groups 1 and 2 will be referred to as "responsive" and "unresponsive" cases in this paper.

When these children are introduced into a 50 per cent oxygen atmosphere, they rapidly begin to develop respiratory difficulty. Within several hours, respiration becomes difficult and asthmatic in type. The rate of respiration increases and the

dence in oxygen was three days and the shortest three hours. In one instance repeated attempts were made to introduce the child into the oxygen chamber with the same unfavorable results.

Effect of Oxygen Therapy. The effect of oxygen therapy was studied from three points of view: (1) the clinical progress of the patient, (2) cardiac manifestations and (3) the progress of rheumatic activity. (Tables I and II.)

1. *Clinical Progress of Patients—Fever:* All the children who showed definite clinical improvement in the oxygen chambers showed a significant drop in temperature. This drop occurred within twenty-four hours of admission in eighteen of the twenty-four patients in this group. The remaining children showed a drop in temperature in four days except in one patient in whom the low grade fever persisted for two weeks. The drop in temperature was in the main either from a low grade fever to normal or from a high normal to a low normal level (99.2°F. to 97.6°F.) All patients showed a significant narrowing of the daily temperature fluctuation. In the “unresponsive” group of children the temperature did not drop from the original level and the daily fluctuation remained unchanged. (Figs. 2 and 3.)

Respiration: Twenty of the twenty-four “responsive” patients showed immediate improvement in respiration. Slowing of the respiratory rate and the relief in dyspnea occurred in most patients within the first twenty-four hours of residence in the oxygen chambers when the evidence of acute carditis and depletion of cardiac reserve (increased venous pressure, prolonged blood circulation time, etc.) remained unaltered. In the remaining four patients the respiratory rate dropped slowly but the depth of respiration increased within the first twenty-four to forty-eight hours of residence in oxygen.* Of the seventeen “unresponsive” patients only five showed a slight and temporary improvement in respiration; seven

* This change in respiratory mechanism is now under study.

TABLE I
OXYGEN THERAPY IN RHEUMATIC CARDITIS IN CHILDREN

	“Re- sponsive” Cases	“Unre- sponsive” Cases
Cases treated		
Number of cases	24	17
Average age for group	11 yr.	10 yr.
Average period of observation	9 mo.	11.5 mo.
Average period of O ₂ therapy	12 wk.	15 wk.
Anatomic { MI	0	2
Diagnosis { MSI	15	8
{ M and A	7	7
Results—number of cases showing:		
1. Clinical improvement		
Drop in temperature	24	0
Drop in respiration	24	5
Weight gain	22	0
Increase in appetite	24	17
Improved facial coloring	24	0
Change in behavior pattern	20	2
2. Change in cardiac manifestations:		
Drop in pulse rate	24	4
Sounds and murmurs	24	2
Angina	6 of 7	2 of 3
Cardiac fatigue	6 of 7	4 of 11
Cardiac insufficiency (subj.)	12 of 13	5 of 7
Heart failure	0
ECG changes	16 of 17	Digitalis?
3. Increase in diuresis	24	0

musical râles in the chest may be heard without the aid of the stethoscope. Within a short time, the patient becomes dusky in color and soon becomes cyanotic. The heart rate rises and the patient becomes restless and anxious. Removal from the oxygen chamber at this point gives almost immediate and complete relief from respiratory difficulty. The heart rate slows rapidly. Restlessness and anxiety subside at once. Of the three children who presented this manifestation, the longest period of resi-

TABLE II
"RESPONSIVE" GROUP

Patient	Before Oxygen Therapy											During Oxygen Therapy										
	Manifestations of Rheumatic Activity											Manifestations of Rheumatic Activity										
	Clinical						Acute Carditis					Clinical						Acute Carditis				
	Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Cardiac	Insuf.	Failure	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Cardiac	Insuf.	Failure
A. H.	+	+	..	-22	+	+	..	+	+	..	+	..	+	+	..	+
B. R.	+	+	..	-45	+	+	+	..	+	..	+	..	+	+	+
C. M.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
C. V.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
C. H.	+	..	-35	+	+	+	..	+	..	+	..	+	+	+
F. A.	+	+	+	+	..	+	..	+	..	+	+	+
G. E.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
G. G.	+	..	-22	+	+	+	..	+	..	+	..	+	+	+
G. S.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
S. A.	+	..	-35	+	+	+	..	+	..	+	..	+	+	+
L. R.	+	..	-15	+	+	+	..	+	..	+	..	+	+	+
L. J.	+	..	-50	+	+	+	..	+	..	+	..	+	+	+
J. V.	+	..	-50	+	+	+	..	+	..	+	..	+	+	+
Q. F.	+	..	-22	+	+	+	..	+	..	+	..	+	+	+
R. G.	+	+	+	+	..	+	..	+	..	+	+	+
R. R.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
R. R.	+	..	-50	+	+	+	..	+	..	+	..	+	+	+
R. B.	+	..	-20	+	+	+	..	+	..	+	..	+	+	+
S. T.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
S. P.	+	..	-20	+	+	+	..	+	..	+	..	+	+	+
S. J.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
S. J.	+	..	-25	+	+	+	..	+	..	+	..	+	+	+
V. M.	+	..	-40	+	+	+	..	+	..	+	..	+	+	+
No. of Cases Changed	5	3	2	13	14	..	20	24	7	7	17	13	20	24	7	6	16	1	1	12

TABLE II—Continued
"UNRESPONSIVE" GROUP

Patient	Before Oxygen Therapy										During Oxygen Therapy																
	Manifestations of Rheumatic Activity										Manifestations of Rheumatic Activity																
	Clinical					Acute Carditis					Clinical					Acute Carditis											
	Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Insuf.	Cardiac	Skin	Joints	Other	Fever	ESR	VC%	Tachycardia	Sounds and Murmurs	Fatigability	Angina	ECG	Insuf.	Cardiac	
A. L.	+	-	..	+	+	+	..	Dig.	+	+	+	-	-	-5	+	+	-	..	Dig.	-	+	
A. A.	+	-	..	+	+	+	..	+	+	+	+	-	-	0	+	+	+	+	
B. H.	+	-	..	+	+	+	..	Dig.	+	+	+	-	-	-50	+	+	Dig.	+	+	
DeM. C.	+	+	..	+	+	+	..	Dig.	+	+	+	-	-	-18	+	+	Dig.	+	+	
F. R.	+	-	..	+	+	+	..	+	+	+	+	-	+	-40	+	+	Dig.	+	+	
F. L.	+	-	..	+	+	+	..	+	+	+	+	-	+	-50	+	+	Dig.	+	+	
L. E.	+	-	..	+	+	+	..	+	+	+	+	-	+	-20	+	+	Dig.	+	+	
M. A.	+	-	..	+	+	+	..	+	+	+	+	-	+	-35	+	+	+	+	+	
O'C. M.	+	+	..	+	+	+	..	Dig.	+	+	+	+	+	-45	+	+	Dig.	+	+	
P. M.	+	+	..	+	+	+	..	Dig.	+	+	+	+	+	-30	+	+	Dig.	+	+	
P. B.	+	+	..	+	+	+	..	+	+	+	+	+	+	-40	+	+	+	+	+	
P. S.	+	+	..	+	+	+	..	+	+	+	+	+	+	-40	+	+	+	+	+	
R. G.	+	+	..	+	+	+	..	Dig.	+	+	+	+	+	-35	+	+	+	+	+	
R. G.	+	+	..	+	+	+	..	+	+	+	+	+	+	-50	+	+	+	+	+	
R. P.	+	+	..	+	+	+	..	Dig.	+	+	+	+	+	-50	+	+	Dig.	+	+	
S. Z.	+	-	..	+	+	+	..	Dig.	+	+	+	+	+	-40	+	+	Dig.	+	+	
M. E.	+	-	..	+	+	+	..	+	+	+	+	+	+	-40	+	+	+	+	+	
Nn. of Cases Changed	14	1	1	6	8	..	15	17	11	3	7	17	13	..	14	0	1	0	6	2	3	2	4	3	4	13	0

+ = the presence of abnormal signs or symptoms.

- = the absence of abnormal signs or symptoms.

Skin = rheumatic erythemas and rheumatic nodules.

Joints = polyarthritis or persistent joint pains.

Other = epistaxis, progressive pallor, abdominal pain, etc.

* Fever = thirteen patients had fever and twenty-four patients showed a drop in temperature either from fever or from a normal level in the "responsive" group.

VC% = the percentage of normal for body surface (vital capacity).

ESR = + elevated and - normal sedimentation rate.

Tachycardia = a rate of 115 or more.

Sounds and murmurs = frequent changes of sounds and murmurs.

Cardiac insufficiency = subjective signs such as dyspnea.

Cardiac failure = objective signs of congestive heart failure: rales in the chest, edema, enlarged liver, increased venous pressure, etc.

ECG = + signifies electrocardiographic deviations from the normal and - signifies no such deviations.

children had no relief from dyspnea, orthopnea or tachypnea and five children showed a moderate increase in respiratory rate. There was no increase in depth of respiration in any of the children in this group.

status or the downward course of the disease. Some children who suffered from acute pancarditis with frank congestive failure had an inordinate increase in appetite during their residence in the oxygen chambers. In this group the appetite

Diagnosis Rheumatic Heart Disease (Acute Carditis)
Mitral Stenosis and Insufficiency
Regular Sinus Rhythm
Class I - E

OXYGEN THERAPY

Gertrude R.
Born 8-13-34
Onset at 5 yrs - Polyarthritis
Three acute episodes

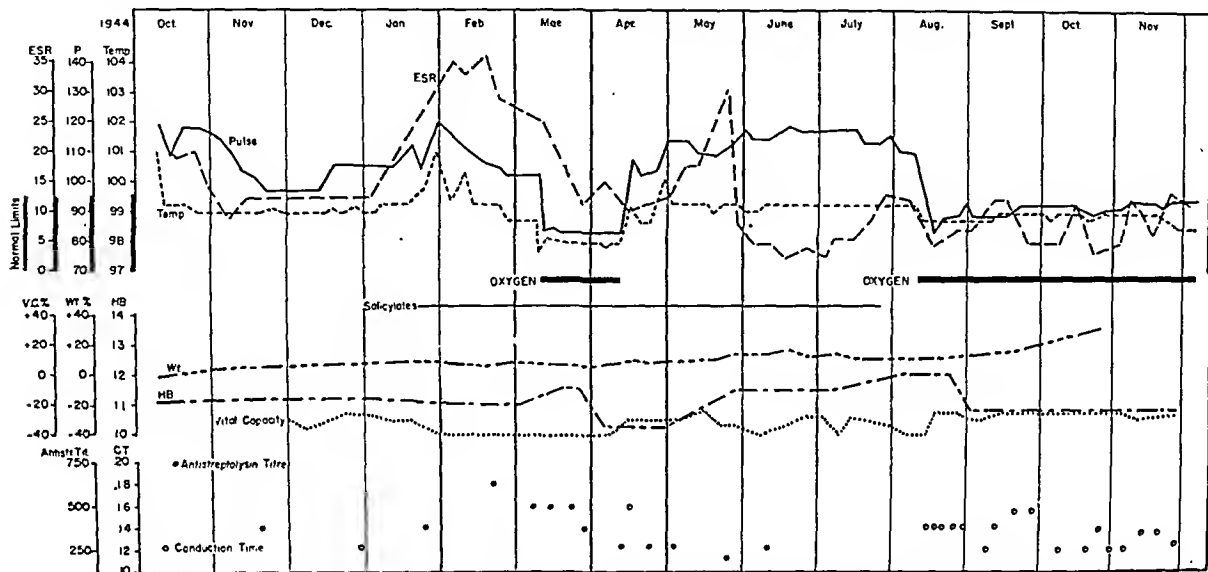


FIG. 2. Chart showing the effect of oxygen therapy upon the clinical course of acute rheumatic carditis. The temperature and pulse curves are smoothed.

Weight Gain:* Of the twenty-four "responsive" patients, twenty-two gained weight at a greater rate than would be expected in a similar group of children with carditis treated routinely outside of the oxygen chamber. The majority of these children began to add weight within one week after oxygen therapy was begun. These showed no such gain for many weeks preceding oxygen therapy. In the "unresponsive" group less than one-half gained slight weight at a slow rate; six children failed to gain during the entire period of observation and four lost a significant amount of body weight.

Appetite: A marked increase in appetite was a common finding among all children who resided in the oxygen chambers. In some instances the increase in appetite was enormous irrespective of the cardiac

failed when oxygen therapy was terminated. In the group of children who improved with oxygen therapy, appetite also decreased when the therapy was stopped, but to a lesser degree than in the "unresponsive" patients.

Complexion: Most children residing in the oxygen chambers showed improvement in facial coloring. This was a late manifestation and did not seem to be related to the changes in hemoglobin level. Facial coloring improved at the time when the hemoglobin level was dropping. In the "responsive" group of patients the increase in facial coloring was often marked although the hemoglobin was dropping. In the "unresponsive" group the improvement in facial coloring was slight and temporary although the hemoglobin level in this group was not depressed.*

* Weight gain is referred to as "dry weight" and not edema.

* Changes in hemic components during residence in 50 per cent oxygen will be discussed in subsequent studies.

Behavior: The “responsive” group of children showed an obvious and significant change in their behavior pattern almost as soon as they were introduced into the oxygen chambers. Irritability, nervousness, impatience and capriciousness changed to obvious contentment, cheerfulness and a sense of peacefulness in most cases within the first twenty-four hours of residence in oxygen. In this group a sense of well being was observed out of proportion to the degree of cardiac disability. While personality differences obviously play an important rôle in adaptation to the discomforts of illness, it is clear from our observations that all children who are benefited by oxygen therapy show an apparent sense of well being as soon as oxygen therapy is instituted. This change in the behavior pattern was not observed among the “unresponsive” group of children. Impatience, resistance to therapy, inimical relationship to doctors and nurses continued unchanged. In this group the degree of emotional upheavals was in the main proportional to the extent of cardiac disability, multiplicity of symptoms and the degree of rheumatic activity.

2. Cardiac Manifestations—Pulse Rate: Twenty of the twenty-four “responsive” patients showed a rapid and dramatic drop in pulse rate. The rate dropped from a moderate tachycardia of 110 to 130 to the normal level of 70 to 90 within twenty four hours of admission to the oxygen chamber. In the other four patients the drop in pulse rate was delayed for several days. The drop in pulse rate was constant and remained at a low level during the entire period of residence in the oxygen chamber. The advent of an intercurrent infection or rheumatic recrudescence raised the pulse rate level only slightly. Emotional disturbance did not disturb the slow pulse rate to any significant degree. The labile character of the pulse rate commonly observed in rheumatic carditis changed to definite stability in this group of patients shortly after the institution of oxygen therapy; the fluctuation in pulse rate was

rarely more than ten points. The stability of the pulse rate continued in all cases after oxygen therapy was discontinued. In the “unresponsive” group of patients there was no drop of pulse rate after oxygen was begun. In some of these children there was

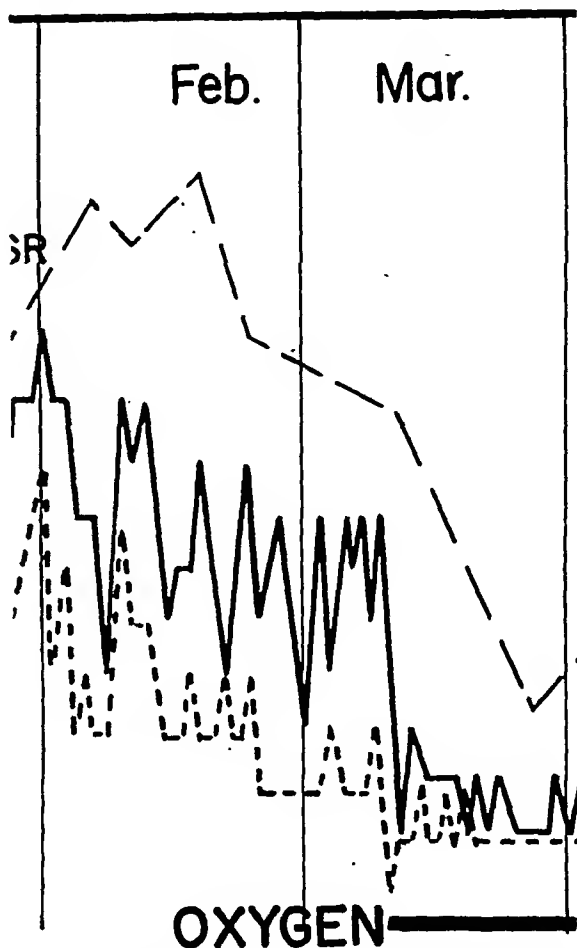


FIG. 3. This is a photographic representation of the temperature and pulse rate chart during the months of February and March. Note the marked fluctuation before oxygen therapy was begun and the minimal fluctuation during therapy.

actually a temporary rise in the heart rate during the first three to six days of residence in oxygen. In a few the pulse rate dropped slightly during the first four days of treatment. The daily fluctuation remained unchanged in the entire group. The labile character of the pulse rate remained unaltered.

*Clinical Carditis*¹⁴—“Responsive” Cases: Of the twenty-four children in this group, twenty-two showed measurable improvement in the functional disturbance of the

acutely inflamed heart during oxygen therapy. Tachycardia, gallop rhythm, tumultuous character of heart action and instability of cardiac rate gradually subsided. While it cannot be said with any degree of assurance that oxygen influenced the course of carditis in this group, functional cardiac disturbances usually associated with acute carditis subsided in this group of patients in a shorter period than would be expected for a similar group of patients outside the oxygen chamber.

"Unresponsive" Cases: Of the seventeen children in this group only two showed similar improvement shortly after admission to the oxygen chamber. The remaining fifteen showed no such improvement and some indeed showed evidence of increase in severity of cardiac disability.

Murmurs—"Responsive" Cases: The frequent changes in quality and mode of transmission of murmurs during the course of acute carditis is well known. In six of the twenty-four children in this group, mitral diastolic murmurs which were heard for long periods of time prior to residence in the oxygen chamber completely disappeared and were not heard for the entire period of observation. In one instance an aortic diastolic murmur disappeared at the end of the period of residence in the oxygen chamber. In a few children of this group the murmurs remained unaltered and in one child evidence of aortic insufficiency developed during the course of treatment. The duration of time during which these auscultatory changes took place varied greatly from patient to patient. In some instances it took many weeks before such changes were effected and in most instances it seemed as if these changes occurred *pari passu* with the cessation of carditis. On the other hand, in several patients these changes took place shortly after oxygen therapy was instituted.

It cannot be stated at this time that these auscultatory changes resulted from the effects of oxygen therapy or were manifestations of the natural course of the progress of acute carditis. It is clear, how-

ever, that these changes were observed more frequently than was found to be the case, in our experience, in a similar group of children treated outside of the oxygen chambers.

"Unresponsive" Cases: In this group of children no auscultatory changes were noted. One child developed a definite mitral stenosis while under treatment; one aortic insufficiency and one tricuspid stenosis.

Anginal Syndrome: Seven children had repeated attacks of anginal pain before oxygen therapy was instituted. The precordial pain was of sudden onset, radiating to shoulders and arms, associated with a sense of anxiety and in most instances was relieved rapidly by the administration of nitroglycerin. In all patients in whom cardiograms were taken during the attack, evidence of anoxemia was noted (depression of S-T segments and T wave changes). Some of these subjects had a marked rise in systolic pressure during the anginal seizure and a marked tachycardia.

All these children showed significant relief from these attacks during residence in oxygen. In some instances the seizures persisted but were of a distinctly milder type. The pain was minimal and the tachycardia somewhat controlled although the associated rise in systolic pressure remained unaltered. None of these children demonstrated the sense of anxiety which was obvious before oxygen therapy was instituted. Six of the seven patients in this group had complete and permanent cessation of this syndrome within one to ten weeks of the onset of oxygen therapy. In one instance several anginal attacks were observed a few weeks after residence in oxygen was discontinued.

Cardiographic Changes—Conduction Disturbances:* In the "responsive" group of patients

* In this study cardiographic changes of three sorts are considered: (1) disturbance in conduction; (2) changes commonly considered indicative of cardiac anoxemia, i.e., S-T segment deviations and temporary T wave changes and (3) changes which we consider as significant of impairment of the integrity of the heart muscle, i.e., prolongation of the electrical systole (Q-T interval).

conduction disturbance observed on the cardiogram subsided rapidly under the influence of oxygen therapy. One child in this group showed a Wenckebach type of block which disappeared within twenty-four hours of residence in oxygen. On the other hand, most of the children in the "unresponsive" group demonstrated conduction disturbances of one sort or another during the course of observation. These disturbances did not seem to be influenced by oxygen therapy. No conclusion, however, can be drawn from this observation since all the children in the latter group were receiving digitalis therapy in addition to oxygen therapy.

Anoxemia Changes: Four children of the "responsive" group showed significant deviations in the S-T segment before admission to the oxygen chambers. All of these deviations subsided within a short period of residence in an oxygen atmosphere. Two of these children showed minimal S-T deviations as soon as oxygen therapy was terminated and in one instance these changes were associated with attacks of precordial pain of an anginal type. In the "unresponsive" group of children S-T and T changes could not be evaluated since these children were digitalized and continued on a maintenance dose during the entire period of observation.

Changes in the Duration of Electrical Systole¹⁷ (Q-T Interval): All children of the "responsive" group had prolonged Q-T intervals at the time oxygen therapy was begun. Many showed a shortening of the Q-T intervals at the end of the period of treatment. Others continued to have prolonged Q-T intervals for weeks and months following oxygen therapy. The shortening of the Q-T interval ran parallel to the subsidence of acute carditis and did not reflect the effect of oxygen therapy upon cardiac efficiency. That digitalis shortens the Q-T interval is well known. Many of the "unresponsive" group of patients were receiving digitalis. Therefore, the effect of oxygen therapy upon the Q-T interval in this group could not be studied.

Diuresis: All children in the "responsive" group showed some increase in diuresis shortly after treatment was begun. In the "unresponsive" group no increase in diuresis was observed. On the contrary the rapidly advancing signs of failure necessitated the active use of mercurials or other diuretics. Furthermore, oxygen therapy did not enhance the diuretic effect of mercurials or digitalis.

3. *Progress of Rheumatic Activity.* The natural history of rheumatic disease does not seem to be significantly altered by prolonged residence in 50 per cent oxygen. Clinical and laboratory evidence of active rheumatic disease continued unabated in the "responsive" and "unresponsive" groups of patients. Many of the clinical manifestations of acute rheumatic fever, i.e., polyarthritides, erythema marginatum, nodules and epistaxis recurred from time to time during the entire period of residence in the oxygen chambers in both groups of children. In the "responsive" group of children, however, rheumatic bouts (joint and skin manifestations, epistaxis, etc.) were not accompanied by an increase in pulse rate, in the tumultuous character of the heart rhythm and by electrocardiographic changes to the same extent as was observed in a similar group of patients not receiving oxygen therapy.

COMMENTS

The primary aim in the treatment and management of rheumatic fever is the prevention of progressive cardiac damage during the course of acute carditis. To this end various forms of therapy have been advocated: prolonged bed rest, sedation, cardiac supportive medication, carefully controlled sanatorial and convalescent care and limitation of physical activities of one sort or another for long periods of time. It must be admitted that despite all such efforts a large group of children suffering from acute rheumatic carditis present greatly damaged hearts at the end of the acute episode. This damage is attributed to a failure to attain effective cardiac rest

during the course of the acute inflammatory process of the myocardium. It is thought that even under the best physical and emotional environment of rest and relaxation the heart muscle is overactive in acute carditis. Overactivity of the acutely inflamed muscle fiber may be responsible for disturbance of the chemical and mechanical integrity of the heart muscle fiber, causing dilatation and further impairment of cardiac efficiency. An accelerated cardiac action may further deplete cardiac efficiency by diminishing diastolic coronary filling, accentuating an already existing anoxemia of the heart muscle. Anoxemia of the heart muscle results in further disturbance of the metabolism of the muscle fiber.

It would seem reasonable to assume, therefore, that a form of therapy which diminishes cardiac overactivity during the course of the acute inflammatory process might prevent the damaging end result of acute carditis. A significant decrease in cardiac rate alone would undoubtedly diminish the work of the heart whose working capacity is already impaired by local tissue anoxia. Decrease in an accelerated cardiac rate might further improve the local tissue oxygen want by improving coronary filling. Finally, this form of therapy might in addition raise the oxygen saturation of the arterial blood which may be critically diminished in these patients.

The observations presented in this paper suggest that oxygen therapy seems to meet these requirements. Cardiac overactivity apparently is diminished. While the duration of rheumatic activity is not measurably shortened by oxygen therapy, the cardiac functional disability associated with acute carditis is greatly reduced. In addition it is obvious that residence in a high oxygen environment during the course of acute carditis removes the disabling and often most troublesome symptom of cardiac fatigue so commonly observed in children suffering from acute rheumatic carditis. The latter symptomatic relief enhances relaxation, sleep and nutrition, factors

which undoubtedly contribute to rapid and satisfactory recovery.

Our experience further suggests that oxygen therapy is of only limited value in rheumatic heart disease of long standing, in which depletion of cardiac reserve presumably is caused mainly by mechanical deficiency of the heart as a pump. In these patients, previous repeated bouts of carditis has resulted in a markedly hypertrophied and dilated heart muscle with low cardiac reserve; the current acute rheumatic process in these patients is only contributory to the failure of a heart which already has a low reserve. Once the muscle fiber has become mechanically deficient, oxygen therapy is of limited value. This observation may explain, in part, the failure of oxygen therapy to produce favorable results in the type of rheumatic heart disease with congestive failure reported by Dr. Barach.^{6a,b, and c} His patients may have been old rheumatic cardiacs with mechanically impaired hearts. Poulton, on the other hand, made his observations in children who had acute carditis. These may have belonged to the group of patients in whom functional cardiac disturbance of the heart was the dominant factor of cardiac disability. In these, oxygen therapy is effective.

SUMMARY AND CONCLUSIONS

1. Forty-four children suffering from acute rheumatic carditis were treated in a carefully regulated oxygen atmosphere of 45 to 50 per cent for long periods of time.

2. The clinical course of carditis was favorably affected in twenty-four of these patients; seventeen patients did not show measurable improvement with this form of therapy and three children showed marked intolerance to the oxygen therapy.

3. The three groups of patients differed clinically in important respects. Criteria for this differentiation have been described.

4. Our observations show that established cardiac damage cannot be reversed by oxygen therapy. They further show that the duration of rheumatic activity is not measurably altered.

5. Our results indicate, however, that oxygen therapy is an important form of treatment in acute rheumatic carditis of the exudative type with minimal mechanical cardiac disability. It reduces significantly the functional cardiac disability associated with acute carditis and favorably affects the clinical symptomatology toward more complete recovery.

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Effect of Oxygen Therapy on the Electrical Sequence of Events in the Cardiac Cycle in Children with Acute Rheumatic Carditis*

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IN a previous communication¹ evidence was presented to show that in children the functional integrity of the heart muscle is impaired in acute carditis. It was further shown that the impairment is expressed in a disturbance of the normal time relationships in the electrical events in the cardiac cycle. The duration of electrical systole (Q-T) is increased both absolutely and relatively to diastole (T-Q). In other words, the duration of contraction† of the heart muscle is prolonged and the period of relaxation is shortened. It was further pointed out that this prolongation in contraction time reflects the degree of functional cardiac disability as measured by the usual clinical manifestations of acute heart disease. The more severe the carditis the longer the duration of systole (Q-T_e).

It was also noted that while the slowing of the speed of contraction may be an expression of the best cardiac effort under the adverse circumstance of the presence of an acute inflammatory process in the heart muscle, such a method of "compensation" is attended by a marked shortening of the period of cardiac relaxation. Diastole (the perfusion time during which chemical balance is restored) becomes abnormally short. A marked decrease in the perfusion time may produce a deficit in the chemical economy of the heart muscle. Thus, the prolongation of the period of contraction

without a commensurate increase in the period of relaxation would seem to be an unprofitable physiologic compensation. The postulate was made that such a faulty cardiodynamic mechanism may contribute to the functional disability of the heart in acute carditis.

It would follow from this observation that a form of therapy which would bring about a normal relationship between the duration of active contraction and the duration of relaxation might restore a more profitable chemical economy in the heart muscle and prevent or reduce the cardiac functional disability of acute heart disease.

Several years' experience with use of oxygen in the treatment of rheumatic carditis in children strongly suggests that this form of treatment given during the exudative phase of acute carditis is an important form of therapy.³ Our observations show that oxygen therapy does not alter the established anatomic cardiac damage but reduces significantly the cardiac functional disability which is present during the acute phase of the disease. There is a marked and rapid drop in heart rate and a decrease in respiratory rate. Precordial pain and evidence of cardiac fatigue subside. In some instances there is an increase in diuresis and a significant drop in the elevated venous pressure. The tumultuous character of the heart action is changed to a quiet and slow rhythm. In addition, the clinical behavior of the

† The electrical and mechanical systoles are considered from the clinical standpoint equivalent in this paper.²

* From the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, N. Y. This study was made possible through grants given by the Life Insurance Medical Research Fund and the Research Department of the Linde Air Products Company.

patient is profoundly changed in favor of a more complete recovery.

This marked clinical improvement in cardiac function prompted us to investigate the effect of oxygen therapy upon the electrical events of the cardiac cycle. The study of the relationship of systole to diastole in patients with acute carditis receiving oxygen therapy forms the thesis of this paper.

MATERIAL AND METHOD OF STUDY

Patients. Fifteen girls ten to fourteen years of age were chosen for this study. All these girls had unequivocal histories of rheumatic fever and during the period of observation had obvious clinical signs and symptoms of rheumatic carditis. Some presented symptoms of cardiac fatigue, others an anginal syndrome and some had incipient signs of heart failure. All patients exhibited the usual laboratory confirmatory evidence of carditis—an elevated sedimentation rate, a depressed hemoglobin and a low vital capacity reading. Several of the patients showed the usual changes on the electrocardiogram—disturbance in conduction and changes in the ST and T segments; all patients presented moderate to marked prolongation of the electrical systole ($Q-T_c$). None of these patients had obvious signs of heart failure during the period of study. Patients with acute pericarditis, marked nutritional disturbance, severe secondary anemias, allergic bronchitis or obvious disturbances in metabolism were excluded from this study.

During the entire period of observation no medication was given to these patients except an occasional sedative for angina or restlessness. None of these patients received digitalis for more than three weeks preceding the period of observation and none received diuretics. The diet was a normal well balanced diet with no salt or fluid restriction.

After a control period of study of not less than two weeks these patients were introduced into an oxygen chamber* where the oxygen concentration was 45 per cent to 50 per cent and the carbon dioxide concentration level fluctuated between 1 per cent and 1.3 per cent. During the control period complete studies were made to evaluate the degree of carditis, to establish a

complete diagnosis and to rule out complications which might introduce new factors in this study. Complete studies were made within the first twenty-four hours after oxygen therapy was begun. Frequent and repeated observations were continued for the entire period of residence in the oxygen chamber.

Graphic Representation. The duration of electrical systole ($Q-T$ interval) varies greatly with the length of the cardiac cycle. Therefore, in order to know whether a given $Q-T$ interval is of normal length or not one must know what the normal length of electrical systole is for a particular rate. This is expressed in Bazette's formula:

$$K = \frac{Q-T \text{ interval in seconds}}{\sqrt{\text{cardiac cycle in seconds}}}$$

K is the constant which expresses the corrected $Q-T$ interval ($Q-T_c$) in terms of cardiac rate. It has been shown that the upper limit of normal $Q-T_c$ for a child is 0.405.⁴ We have shown elsewhere¹ that in children with rheumatic carditis the prolongation of electrical systole ($Q-T$) bears a distinct relationship to the degree of disturbance in cardiac function resulting from carditis and not to the cardiac rate. In other words, the degree of disturbance in cardiac function in carditis is measured in the disturbed time relationship between systole and diastole. The longer the duration of systole as related to diastole the more severe the carditis.

In order to evaluate the severity of carditis in our patients treated with oxygen a graphic representation was made upon which was plotted the relationship of systole to diastole at varying cardiac rates and varying degrees of carditis as expressed by the prolongation of ($Q-T_c$). (Fig. 1.)

The ordinate represents varying quotients of $\frac{Q-T}{T-Q}$ as measured directly on the electrocardiogram. The abscissa represents cardiac rates ranging from 70 to 136. The curves on the graph were obtained by connecting multiple points representing the quotients of $\frac{Q-T}{T-Q}$ calculated for corrected $Q-T$ s (K)* ranging from 0.36 to 0.49 at cardiac rates ranging from 70 to 136. Thus, the quotient $\frac{Q-T}{T-Q}$ in a case of carditis with a corrected $Q-T$ of 0.49 and a cardiac rate

* This chamber has been described elsewhere.³

* K and $Q-T_c$ are used interchangeably.

of 136 is 2.81. In the same patient with the same degree of carditis but at the cardiac rate of 70 the quotient is 1.15. The shape of the curves is explained in the following manner: the convergence of the curves at slow cardiac rates and the divergence of the curves at high

$$K = \frac{Q-T \text{ in seconds}}{\sqrt{R-R} \text{ in seconds}}$$

$$Q-T = K\sqrt{R-R}$$

$$T-Q = R-R - Q-T \text{ in seconds;}$$

therefore,

$$\frac{Q-T}{T-Q} = \frac{K\sqrt{R-R}}{R-R - K\sqrt{R-R}} \text{ or } \frac{K\sqrt{R-R}}{\sqrt{(R-R)^2 - K\sqrt{R-R}}} \text{ or } \frac{K}{\sqrt{R-R} - K}$$

The larger the K and the smaller the denominator the greater the quotient; the smaller the K and the larger the denominator the smaller the quotient.

RESULTS

All of the fifteen patients studied presented similar changes in regard to the relationship of systole to diastole shortly after oxygen therapy was instituted. (Figs. 2 to 17.) An analysis of these graphs will show that in each case cardiac rate was decreased and there was a rapid return to a more normal relationship of systole to diastole when oxygen therapy was begun. This was attained in all patients not by significant shortening of the systolic period (Q-T) but rather by a marked lengthening of the diastolic period (T-Q). In some instances the increase in duration of diastole was many times that of systole. This occurred in all cases irrespective of the time it took to effect the result after oxygen therapy was instituted.

In some cases this was attained within the first twenty-four hours of oxygen therapy; in others, a longer period was required to bring about a similar result. Those patients who showed evidence of myocardial damage such as deviations of the S-T interval and distortions in the T wave required a longer period of oxygen therapy before clinical improvement became manifest and a more normal relationship of systole to diastole was attained. In these cases the electrocardiographic signs of cardiac anoxia subsided first. In some, the electrical systole became longer as the S-T segments returned to the iso-electric

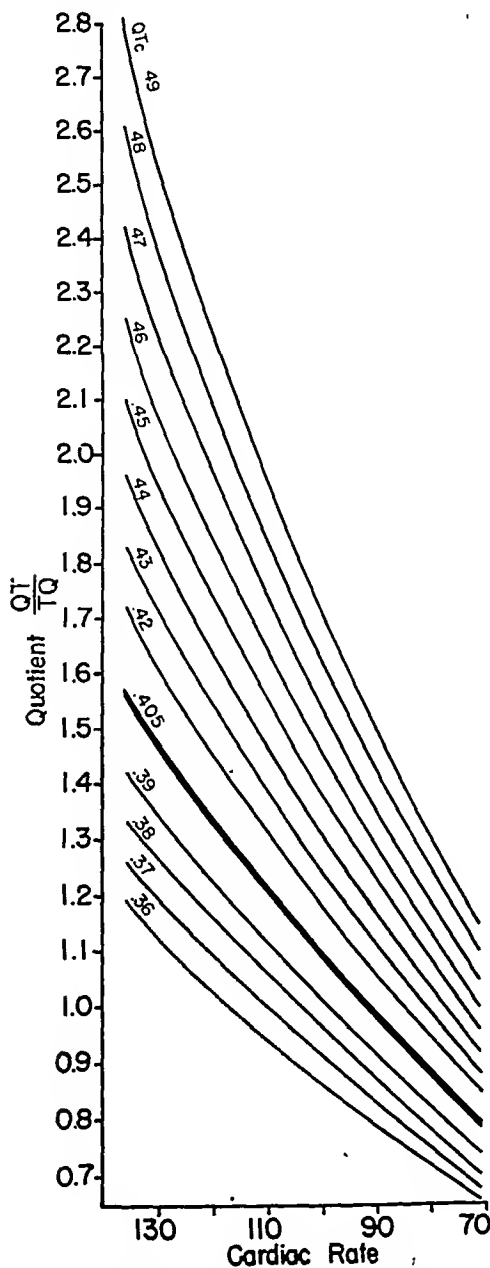
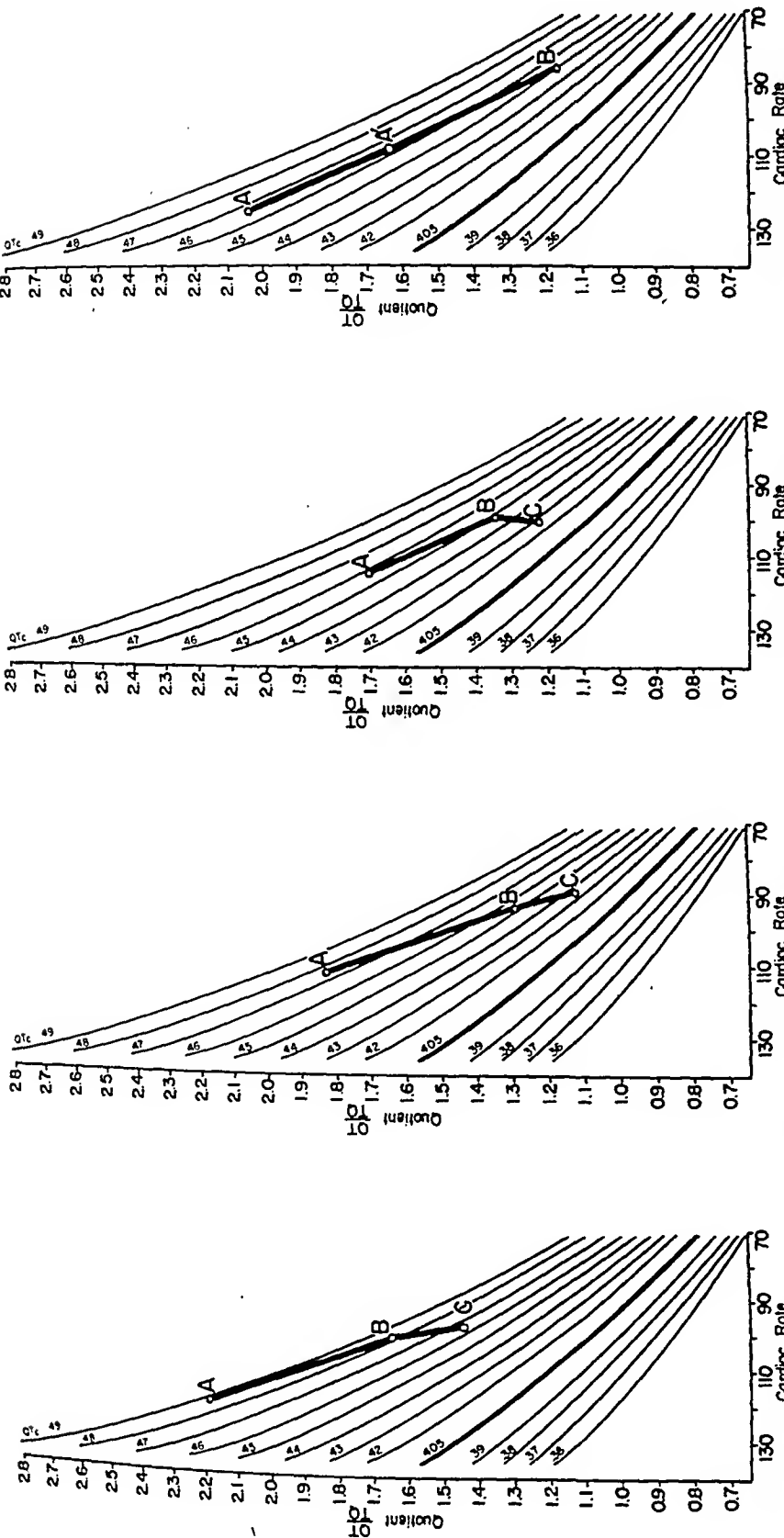


FIG. 1. This is a graphic representation upon which is plotted the relationship of systole to diastole at varying cardiac rates and varying degrees of carditis as expressed by the prolongation of the QTc.

cardiac rates is derived from the nature of Bazette's formula since the significant change in the formula at various cardiac rates is the length of the cardiac cycle.



Date	EKG	Rate (in sec)	Measured QT	QTc	QTc (in sec)	QTc (in sec)
12/13/46	A	127	32	155	206	465
3/6/47	A'	105	352	217	1.61	463
3/26/47	B	87	374	317	1.17	45
P.M. - Female, 8 years Diagnosis: R.H.D.-active, M.S.I.						

FIG. 5. Case 4

Date	EKG	Rate (in sec)	Measured QT	QTc	QTc (in sec)	QTc (in sec)
7/1/47	A	115	33	188	175	457
7/11/47	B	99	35	256	135	448
9/27/47	C	101	328	264	124	428
DeC. J. - Male, 8 years Diagnosis: R.H.D.-active, M.S.I., A.S.I.						

FIG. 4. Case 3

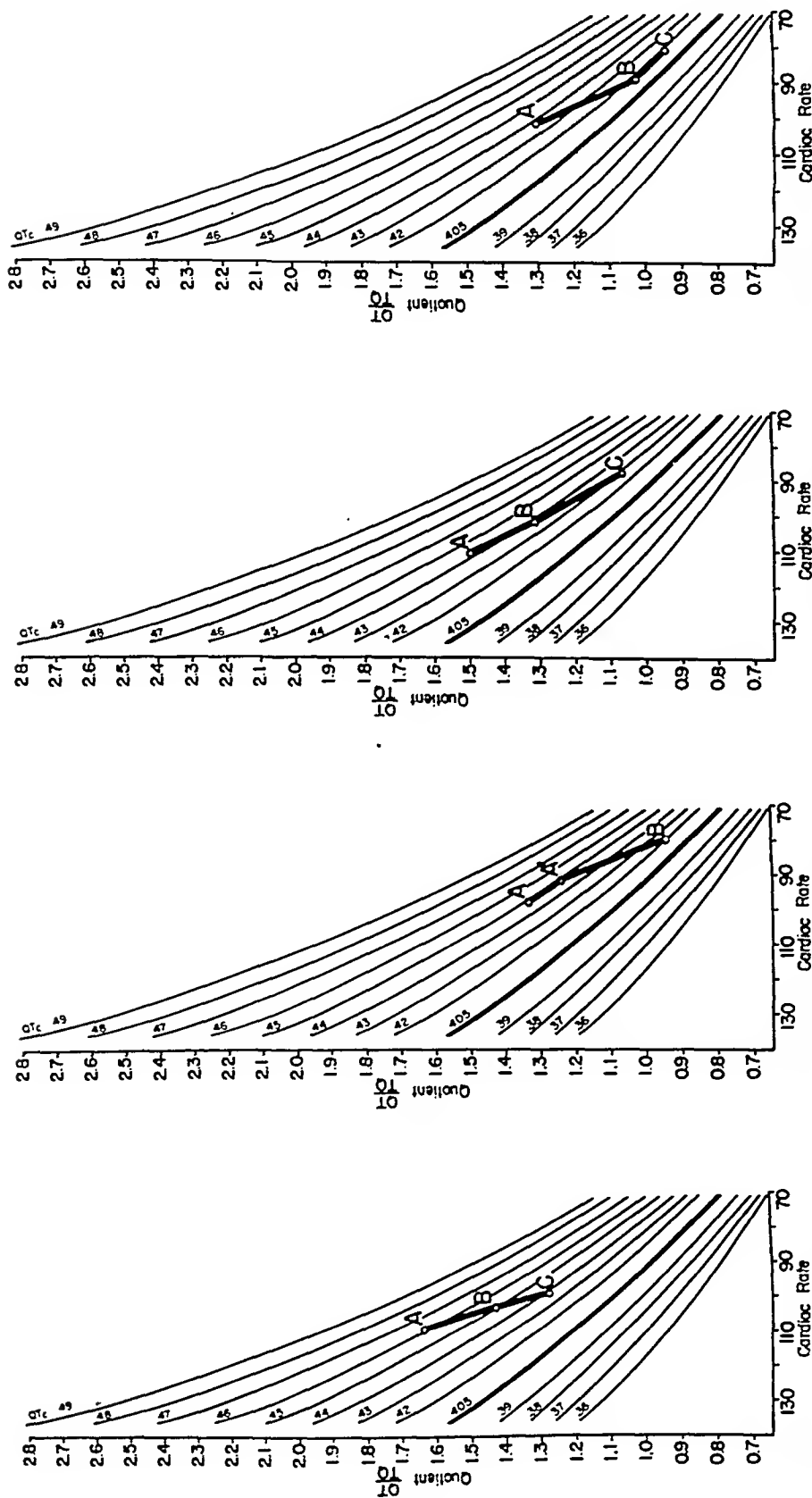
Date	EKG	Rate (in sec)	Measured QT	QTc	QTc (in sec)	QTc (in sec)
5/9/47	A	113	344	184	187	475
6/30/47	B	93	367	279	131	452
7/15/47	C	89	357	312	114	435
C.D. - Female, 8 years Diagnosis: R.H.D.-active, M.S.I.						

FIG. 3. Case 2

Date	EKG	Rate (in sec)	Measured QT	QTc	QTc (in sec)	QTc (in sec)
6/13/47	A	119	346	156	221	487
6/17/47	B	103	368	212	174	481
9/20/47	C	97	365	252	144	465
M.R. - Female, 14 years Diagnosis: R.H.D.-active, M.S.I.						

FIG. 2. Case 1

For legends see page 399.



Date	EKG	Rate at 1 to 2	Measured Rate (in sec) QTc	Quotient (in sec) QTc	Days in O ₂
8-19 A 47		110	34	202/68	.46
9-11 B 47		104	339	234/145	.45
9-20 C 47		100	338	262/129	.436
N.A. - Male, 7 years Diagnosis: R.H.D.-active, M.S.I.					

FIG. 6. Case 5

Date	EKG	Rate at 1 to 2	Measured Rate (in sec) QTc	Quotient (in sec) QTc	Days in O ₂
3-16 A 46		98	349	265/131	.448
3-23 A 46		92	358	292/123	.448
4-30 B 46		80	364	394/95	.42
F.A. - Female, 6 years Diagnosis: R.H.D.-active, M.S.I.					

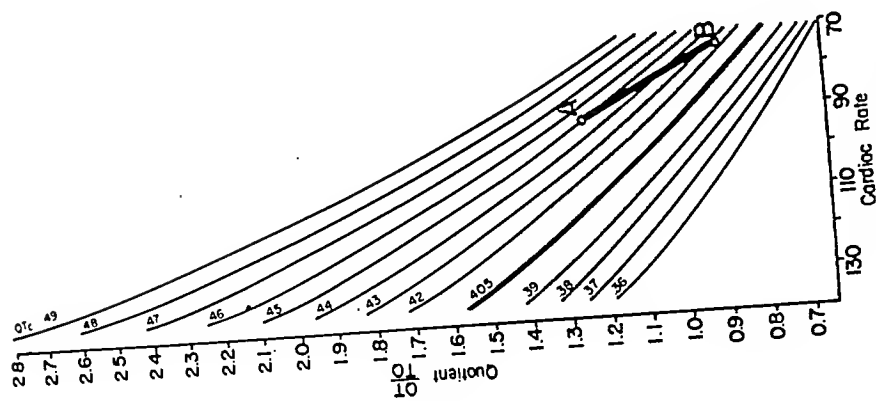
FIG. 7. Case 6

Date	EKG	Rate at 1 to 2	Measured Rate (in sec) QTc	Quotient (in sec) QTc	Days in O ₂
7-2 A 47		111	325	213/153	.442
7-4 B 47		102	338	25/135	.439
7-11 C 47		88	352	33/106	.428
G.J. - Male, 8 years Diagnosis: R.H.D.-active, M.S.I.					

FIG. 8. Case 7

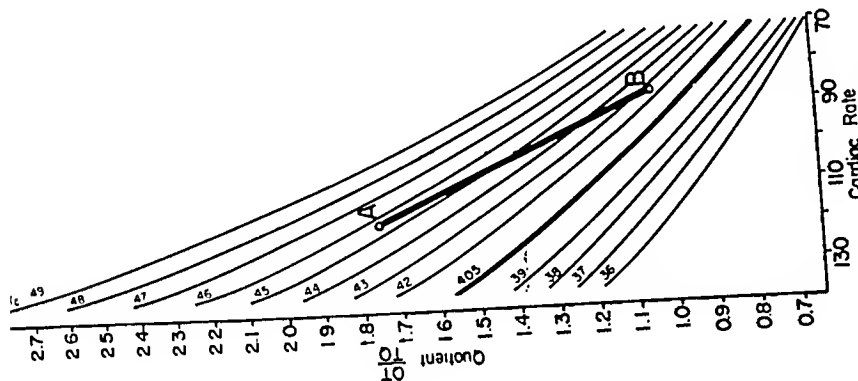
Date	EKG	Rate at 1 to 2	Measured Rate (in sec) QTc	Quotient (in sec) QTc	Days in O ₂
3-15 A 46		102	336	254/132	.436
3-19 B 46		89	342	328/104	.415
6-6 C 46		82	356	372/95	.416
G.G. - Female, 13 years Diagnosis: R.H.D.-active, M.S.I.					

FIG. 9. Case 8



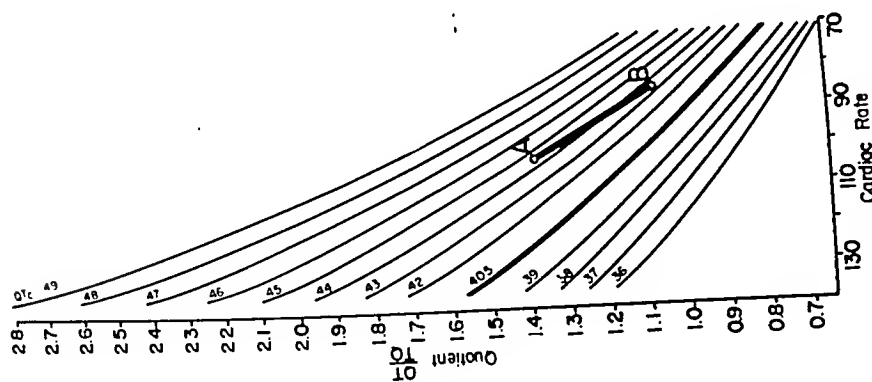
Date	EKG	Rate	Measured QT (in sec)	QTc (in sec)	Days in QTc
221 A 46		92	364	284	127
42 B 46		75	38	408	91
Q.F. - Female, 13 years Diagnosis: R.H.D.-active; MSI.					

Fig. 13. Case 12



Date	EKG	Rate	Measured QT (in sec)	QTc (in sec)	Days in QTc
1026 A 46		118	327	183	178
116 B 46		87	354	334	105
F.M. - Female, 12 years Diagnosis: R.H.D.- active; MSI.					

Fig. 12. Case 11

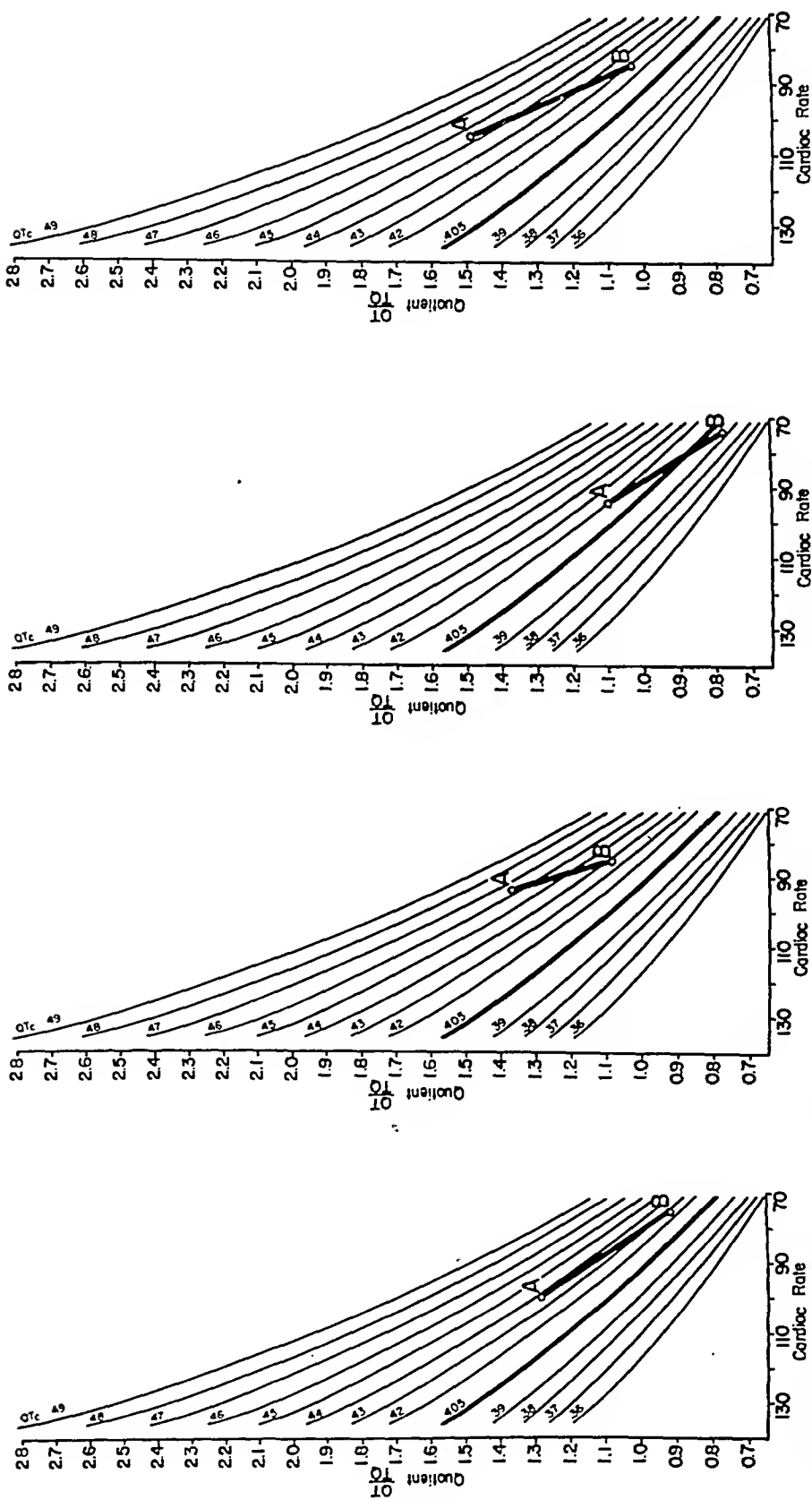


Date	EKG	Rate	Measured QT (in sec)	QTc (in sec)	Days in QTc
422 A 47		102	342	248	138
430 B 47		86	362	336	108
B.J. - Female, 12 years Diagnosis: R.H.D.-active; MSI.; A.I.					

Fig. 11. Case 10

Date	EKG	Rate	Measured QT (in sec)	QTc (in sec)	Days in QTc
429 A 47		130	306	154	198
430 B 47		104	348	226	154
58 C 47		93	351	297	118
630 D 47		91	34	32	106
P.C. - Female, 10 years Diagnosis: R.H.D.-active; MSI.					

Fig. 10. Case 9



	Rate	Measured QT (in sec)	Quotient QT/TA	Days in O ₂
A	106	.341	.221	1.54
B	86	.358	.339	1.05
AVERAGE of 15 CASES				
				36

FIG. 17.

Date	EKG	Rate	Measured QT (in sec)	Quotient QT/TA	Days in O ₂
6-4-46		94	.334	.302	1.1
7-18-46		74	.352	.454	.76
J.B. - Female, 9 years Diagnosis: RHD-mildly active; M.I.					
					392
					13

FIG. 16. Case 15

For legends see page 399.

Date	EKG	Rate	Measured QT (in sec)	Quotient QT/TA	Days in O ₂
6-3-47		93	.37	.276	.132
6-17-47		86	.366	.33	.111
A.A. - Female, 6 years Diagnosis: R.H.O.-active; M.S.I.					
					463
					439
					13

FIG. 15. Case 14

Date	EKG	Rate	Measured QT (in sec)	Quotient QT/TA	Days in O ₂
1-9-46		100	.34	.26	.13
1-12-46		75	.382	.418	.91
S.T. - Female, 7 years Diagnosis: RHD-active; M.S.I.					
					428
					2

FIG. 14. Case 13

FIGS. 2 to 16. Graphic representations of the change in electrical events within the cardiac cycle in each of the fifteen patients treated with oxygen during the course of acute carditis. The heavy curved line marked 0.405 represents graphically the $\frac{QT}{TQ}$ relationship at a QT_c (K) of 0.405. All

curved lines above this level represent abnormal $\frac{QT}{TQ}$ relationships found in cases of carditis; those below this level represent a normal $\frac{QT}{TQ}$ relationship found in

normal children with quiescent rheumatic heart disease. The heavy lines connecting the open circle represent graphically the $\frac{QT}{TQ}$ relationship in each of our cases at several stages of therapy: (A) before oxygen; (A') before oxygen therapy was started but at a later date; (B) shortly after oxygen therapy was begun; (C) after oxygen therapy was continued for a variable period of time; (D) at a still later date. A close analysis of these graphs shows the following:

1. In cases in which the rheumatic carditis continues the abnormal relationship of systole to diastole remains unaltered even though the heart rate may become slower. This is expressed in the fact that the QT_c remains unchanged. When such patients are introduced into a high oxygen atmosphere, the pulse rate may or may not drop further but there is a distinct change in the relationship between systole and diastole. This is attained primarily by a lengthening of the diastolic period. (See Case 4, Fig. 5 and Case 6, Fig. 7.)

2. The heart rate drops measurably shortly after beginning oxygen therapy in patients with carditis, but the relationship of systole to diastole as expressed in the QT_c may remain either completely unaltered or only slightly changed in the direction of normal. As oxygen therapy is continued for only a few days, the heart rate in most instances continues to decrease. The important change, however, occurs in the relationship of systole to diastole. The QT_c becomes shortened. This is attained by a marked prolongation of the diastolic period even at the time when the systolic period is either completely unchanged or only slightly prolonged. (See Figs. 2, 3, 6, and 8 to 16 inclusive.) In instances in which there is no drop in cardiac rate there is still a restoration to a more normal relationship of systole to diastole. (Fig. 4.)

3. It is noteworthy that electrocardiographic signs of anoxemia as expressed by deviations of the S-T and T segments subside almost as soon as oxygen therapy is instituted. (See Figs. 2, 11, 15 and 16.)

FIG. 17. Represents the average of the fifteen patients. The average number of days of oxygen therapy at the time of the most significant change is 36. For the entire group of cases the change in pulse rate after oxygen therapy was instituted was from an average of 106 to 86. The average increase in the duration of the systolic period was small (from 0.341 to 0.339). This brought the ratio of systole to diastole to a more normal relationship (from 1.54 to 1.05).

line. At this phase the cardiac rate became slow and the diastolic period became significantly prolonged.

All patients showed unequivocal clinical improvement* as the electrical sequence of events approached a more normal relationship. It may be stated that in those instances in which the patient was removed from the oxygen room shortly after these apparent beneficial effects were attained, a reversal of the progress at once became manifest. The cardiac rate increased and the relationship of systole to diastole returned to the level observed before oxygen therapy was begun. In those instances in which oxygen therapy was prolonged for several weeks beyond the point of apparent improvement the benefits seemed to persist. Each patient in our present series seemed to require an individual period of oxygen therapy before the apparent beneficial effects became permanent. It is hoped that further experience with this form of therapy will bring to light criteria which might help in the decision as to how long oxygen therapy should be continued.

COMMENT

In our experience the sequence of events in the progress of cardiac disability in acute carditis in children usually follows a distinct electrocardiographic and clinical pattern. In the acute exudative phase, when the heart is acutely inflamed, the tumultuous cardiac action is expressed in a delay in the period of heart muscle contraction at the expense of the period of relaxation. The more severe the clinical carditis the longer the duration of contraction and the shorter the period of relaxation. When the period of relaxation becomes abnormally short, the patient begins to show some subjective signs of cardiac insufficiency, such as dyspnea on exertion, cardiac fatigue, etc. At this stage the electrocardiogram usually shows signs of anoxia. In cases in which the electrocardiographic evidence of anoxemia

continues for a long period of time other evidence of progressive cardiac disability may become manifest. Some patients begin at this stage to develop various forms of disturbance in rhythm—premature contractions, paroxysmal auricular flutter, paroxysmal auricular fibrillation, etc. Other patients continue to develop further cardiac dilatation and hypertrophy and finally begin to show objective evidence of congestive heart failure.

Our observations would seem to show that the administration of oxygen during the early anoxic phase of acute carditis favorably influences the course of acute carditis. The mechanism by which oxygen therapy produces these apparent beneficial effects is not clear. If we are to assume that an increase in the oxygen saturation of the arterial blood may help to prevent or improve local tissue anoxia, inhalation of an oxygen-enriched atmosphere containing 45 per cent to 50 per cent oxygen would be expected to raise the oxygen saturation of the arterial blood in cardiac patients, restoring the oxygen tension and presumably in this way reversing the ill effects of anoxemia. Whether this mechanism may play a part in effecting improvement in the functional disability of the heart during the course of acute carditis is now under investigation.

The observations presented here show that oxygen therapy decreases cardiac overactivity and that the heart action approaches a more normal tempo even with persistence of acute carditis. This is apparently accomplished by restoring a more normal relationship in the duration of systole to that of diastole. This restoration may be effected by decreasing the duration of systole or by lengthening the duration of diastole. As shown elsewhere¹ systole occupies a relatively smaller portion of the cardiac cycle as carditis subsides and thus the relationship of systole to diastole becomes more normal. In oxygen therapy, however, the diastolic period becomes very much prolonged while the duration of

*The nature of clinical improvement has been described elsewhere.²

systole is only slightly altered. The restoration to a normal relationship is accomplished by the device of lengthening the diastolic period.

It is reasonable to postulate that an increase in the period of relaxation (perfusion time) might improve the chemical economy of the heart. And it is noteworthy that this mechanism is attained without disturbing measurably the delay in contraction which may be a compensatory response of the acutely inflamed heart muscle.

It obviously cannot be said from these observations that oxygen therapy significantly and rapidly influences the acute inflammatory process in the heart in acute carditis. On the other hand, it seems apparent that the functional disturbance of the heart action resulting from a shortening of the period of cardiac relaxation and a lengthening of the period of contraction is significantly improved even while the inflammatory process continues. The effect of this improvement upon total cardiac disability resulting from rheumatic carditis forms the subject of further investigation.

SUMMARY AND CONCLUSIONS

1. Fifteen representative cases of acute rheumatic carditis in children who showed definite clinical improvement with oxygen therapy are analyzed.

2. All patients showed a return of the Q-T:T-Q ratio in the direction of normal when oxygen therapy was instituted.

3. Restoration of a normal systolic: diastolic ratio was attained by prolongation of the diastolic period while the systolic period remained unchanged.

4. It is believed that improvement in the functional cardiac disability of acute carditis observed in oxygen therapy may prevent further cardiac damage during the acute phase of carditis.

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The Treatment of Pneumococcal Meningitis*

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THE past decade has witnessed remarkable progress in the therapy of many of the common bacterial infections. Not among the least of the accomplishments of these years have been improvements in the management of purulent meningitis. With the emergence in rather rapid succession of antisera, sulfonamide derivatives and penicillin, it is appropriate to survey the results which have been obtained with these agents singly and together in situations in which they have proved partly or outstandingly effective. It is the purpose of this review to detail the experiences of this and other clinics in the therapy of infections of the meninges due to the pneumococcus. In examining reports of a large number of cases, opportunity was afforded to collect statistics on the course of the disease as modified by therapy. While little of this information is new, confirmation on the basis of a fairly large number of cases appears worth while.

As a cause of meningitis the pneumococcus is exceeded in frequency by the *Mycobacterium tuberculosis* and the meningococcus; it is usually stated to be slightly more common than the hemolytic streptococcus. In a series of approximately 5,000 subjects collected by Kcefer,¹ the offending organism was *M. tuberculosis* in about 1,500 and meningococcus in 2,000 while the pneumococcus was isolated from slightly over 500 patients and the hemolytic streptococcus from about 400.

It is known that the pneumococcus may gain access to the meninges from adjacent foci of suppuration such as the middle ear,

or by hematogenous extension from the lungs. Infection also commonly arises in the absence of demonstrable foci but sometimes enters through skull fracture, either traumatic or operative. Linell and Robinson² have reported cases of pneumococcal meningitis developing years after head injury. Organisms appeared to have entered through old fracture lines where bony union had failed to occur. Finland,⁷ Toomey,⁸ Rhoads¹⁰ and Hartman¹⁴ have described a number of patients with pneumococcal meningitis with a remote history of skull fracture or head injury.

Reference to Table I shows that in a total of 409 patients meningitis resulted from extension of infection in the ears or mastoid bones in 151, as a primary disease in 122, followed pneumonia in 101 and resulted from traumatic skull fracture in nineteen patients. Sinusitis occurred as the initial infection in thirteen subjects while meningitis resulted three times after cranial operation (brain tumor once, nasal cavity twice). It is of interest that while about 25 per cent of all cases appearing in the table arose from pre-existing pulmonary infection, the disease is actually an uncommon complication of pneumonia, the incidence according to Heffron³ being between 0.4 and 1.9 per cent.

Invasion of the meninges by the pneumococcus occurs at all ages and the distribution in 249 patients is given in part B of Table I. Children in the first decade appear to be attacked twice as often as any other group, over one-fourth of the total, according to recent reports occurring in the first two years of life. Undoubtedly this is an expres-

* From the Haynes Memorial and Evans Memorial, Mass. Memorial Hospitals and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

sion of the frequency of middle ear and mastoid disease in young children.

In 433 cases the serologic type of the offending pneumococcus was stated and these are shown in part D of Table I where it is seen that half of all cases were caused

by the first eight types and another fourth by types 12, 14 and 18. It is of interest that types 4 and 6, which do not often cause lobar pneumonia, were isolated as often as those more commonly associated with pulmonary infection.

Consideration of clinical and laboratory diagnostic features of pneumococcal meningitis is beyond the scope of this review. However, in cases of intracranial disease following infection elsewhere in the body, certain conditions other than meningitis must be considered if the neurologic and spinal fluid findings are atypical. Reference is made to the important paper of Kubik and Adams^{2a} who re-emphasize the syndrome of subdural empyema which is a neurosurgical emergency.

Before 1936 almost all cases of pneumococcal meningitis resulted fatally. Therapy was confined principally to surgical attack on infected foci and constant or intermittent drainage of the subarachnoid space. Several substances, including various dyes and (later) ethyl hydrocupreine, were employed as possible antibacterial agents. While the latter may have been of some value in certain local infections due to the pneumococcus, none of these drugs influenced the mortality in patients with meningitis. Specific antipneumococcus horse serum may have produced isolated recoveries but regularly successful therapy was delayed until the advent of the sulfonamide derivatives. Goldstein and Goldstein⁴ in 1947 collected from world literature 150 reports of recoveries from what they believed to be pneumococcal meningitis. Vogelius,¹² however, re-examined the original reports, available in twenty-two instances, and was unwilling to accept the diagnosis in any of these. The outlook in the presulfonamide era is perhaps better depicted in part E of Table I in which 631 case reports have been collected. Of these there was only one recovery.

In 1936 a few patients with various infections were treated with azosulfamide and prontosil; shortly thereafter sulfanilamide became available to be followed within a

TABLE I
PNEUMOCOCCAL MENINGITIS

A. Origin of Meningitis in 409 Cases		
Site of Origin	No. of Cases	
Middle ear and mastoid disease.....	151	
Primary.....	122	
Pneumonia.....	101	
Skull fracture.....	19	
Sinusitis.....	13	
Cranial operation.....	3	
B. Age Incidence in 249 Cases		
Age	No. of Cases	
0- 2.....	74	
2-10.....	35	
10-20.....	30	
20-30.....	14	
30-40.....	3	
40-50.....	35	
50-60.....	46	
60.....	12	
C. Blood Cultures in 201 Cases		
Positive.....	117	
Negative.....	84	
D. Serologic Type of Pncumococcus in 433 Cases		
Type	Per Cent of Cases	
1.....	7	
2.....	2	
3.....	13	
4.....	6	
5.....	7	
6.....	6	
7.....	6	
8.....	3	
	50	
12.....	6	
14.....	7	
18.....	9	
	22	
All others.....	28	
E. Mortality in Pncumococcal Meningitis Prior to the Use of the Sulfonamides		
Clinic	Total Cases	No. of Re-coveries
Charity Hospital, New Orleans ¹⁹	111	1
Cleveland City ⁸	157	0
Sydenham ⁹	29	0
Children's, Washington ²⁰	50	0
Harriet Lane Home ³⁹	150	0
Children's, Boston ³⁰	35	0
Boston City Hospital ⁷	99	0
Total.....	631	1

year by sulfapyridine. During this period more or less concentrated rabbit antiserum began to be marketed for use against an increasing number of common serologic types of pneumococcus. By the summer of 1937 reports of successfully treated pneumococcal meningitis began to appear and it soon became apparent that certain patients with this hitherto uniformly fatal infection could be cured. In 1941 Steele and Gottlieb⁵ were able to collect data on 115 patients among whom there were sixty-nine recoveries. This review contains references to the earliest reported patients treated with sulfonamides. Fifty-seven of these patients were given sulfanilamide while sixty-eight were treated with sulfapyridine. No important difference was noted in the efficacy of the two drugs. The value of specific antiserum, also administered to twenty-six patients of the whole group, will be discussed later. Steele and Gottlieb anticipated the objection of later writers that the recovery rate of 60 per cent was too high. Their material contains numerous papers describing only two or three patients with 100 per cent survival, and such a compilation necessarily omits small groups of therapeutic failures which are less likely to be published. The same criticism applies to the earlier review of Coleman⁶ who arrived at a recovery rate of 69 per cent in reports collected from British literature. In surveying publications subsequent to these papers it was decided to consider only those reports describing six or more patients in order to determine more accurately the true experience with sulfonamides. Smaller groups were accepted, however, when they were presented as parts of a series treated by more than one method. This was done in order to include early penicillin results published by authors reporting numerous sulfonamide-treated patients and appending accounts of penicillin in the limited number of patients for whom it was at first available.

No effort was made to eliminate patients who died very early after treatment was begun, nor were patients separated on the basis of which sulfonamide drugs were

employed. No evaluation was made of various methods of spinal fluid drainage employed in some of the material examined, nor was account taken of the minority of subjects receiving intrathecal injection of solutions of sulfonamide.

Table II contains recovery rates from 196 well described reports of sulfonamide-treated patients which have appeared since 1940.* These values range between 0 and 40 per cent; the best results are less than the 60 per cent survivals estimated by Steele and Gottlieb. The average of 25 per cent is significantly lower for reasons already given. In Table III detailed analysis of 181 subjects is presented. Certain of the reports from Table II are omitted because data were incomplete or were not analyzed in the same manner as in Table III. The patients of Finland, Toomey and the first series of Hodes were included in the review of Steele and Gottlieb, but are introduced into Table III because they represent thirty-nine well described patients. Of interest is the fact that the gross recovery rate of this new group is 29 per cent, not differing significantly from the 25 per cent of Table II.

The series of Finland, with 60 per cent survivals, is the sole report which equals the rate calculated by Steele and Gottlieb. All authors in describing pneumococcal meningitis have remarked upon the variation in results encountered from one clinic to another, suggesting the possibility of "mild," "moderate" and "severe" cases. The non-existence of mild or moderate pneumococcal meningitis is documented in part E of Table I. It is, however, true that the response to therapy is significantly altered by certain factors, some of which may be identified in Table III. At once apparent is the influence of the patient's age. While fourteen of twenty-nine patients between two and ten

* Seventy-three patients with four recoveries reported by Dowling¹⁶ and his colleagues are not included. These were collected from the files of various hospitals and some were neither treated nor seen by the authors. It is not believed that they represent the results which may be obtained with sulfonamides under the most favorable conditions. This paper, however, was a valuable addition to the material presented in Table I.

years were successfully treated with sulfonamides, only four of twenty-eight infants under two recovered. The outcome was favorable in nearly one-third of patients between thirty and fifty, whereas only about one-eighth past fifty were cured. The

TABLE II

RECOVERY RATES IN COLLECTED CASES OF PNEUMOCOCCAL MENINGITIS TREATED WITH SULFONAMIDES

A. Patients Treated with Sulfonamides with or without Antiserum

Author	No. of Cases	Recoveries, Per Cent
Steele and Gottlieb ⁵ (collected cases) . .	115	60
Rhoads ¹⁰	22	32
Neal	30	33
Vogelius ¹²	18	22
Feldman ¹³	6	0
Hartman ¹⁴	26	35
Hodes (second series)	43	40
Sweet ¹⁵	40	8
Weller ¹⁸	11	0
Ross ³⁵	54	22
Total since Steele and Gottlieb	250	25

B. Patients Treated with Sulfonamides Alone

Author	No. of Cases	Recoveries, Per Cent
Steele and Gottlieb (collected cases) . .	89	57
Subsequent reported cases	98	27
Total	187	41

C. Patients Treated with Sulfonamides and Specific Antiserum

Author	No. of Cases	Recoveries, Per Cent
Steele and Gottlieb (collected cases) . .	26	69
Subsequent reported cases	140	35
Total	166	42

TABLE II—(Continued)

D. Patients under Age Two Years Treated with Sulfonamides with and without Specific Antiserum

	Cases	No. of Recoveries
Without serum	23	1
With serum	33	10

E. Comparison of Results with Sulfonamides and with Penicillin (with or without Sulfonamides) in Cases in Which the Prognosis Is Known to Be Poor

	Sulfonamides		Penicillin	
	No. of Cases	Recoveries, Per Cent	No. of Cases	Recoveries, Per Cent
Patients under age 2	28	14	58	69
Patients over age 50.	15	13	67	34
Meningitis following pneumonia	40	13	41	47

survival rate of only 20 per cent in the age group twenty to thirty is of doubtful significance since only eight patients in this decade were reported; and of this small number several were complicated, since there are included a pregnant female with pneumonia and two persons with head injury.

Steele and Gottlieb, as well as most of the clinicians who have described their cases subsequently, have expressed the view that prognosis is not greatly influenced by demonstration of pneumococcal bacteremia during meningitis. Ninety-five blood cultures were reported in the sulfonamide-treated patients and about half were positive. Of these, 32 per cent survived while, of those from whom the organism was not isolated, 45 per cent recovered. Thus, invasion of the blood stream alters the outlook only slightly if at all. Of great importance, on the other hand, was the source of meningeal infection. Disease of the middle ear or mastoid was the precursor of meningitis in over a third of the recorded

instances and the incidence of recovery was 36 per cent. To avoid the introduction of an additional column into Table III, three patients with sinusitis with aural and mastoid infection are included. In a somewhat smaller number of patients no focus could

These factors explain, in part, some of the unusual therapeutic results recorded in the literature. In Finland's group with 60 per cent cures there were no infants, no patients over the age of fifty and only one with pneumonia. On the other hand, Feldman,

TABLE III

ANALYSIS OF 181 CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH SULFONAMIDES WERE USED

Author	Totals	Age Group in Years							Blood Culture		Pathogenesis of Meningitis					Other Rx		Additional Lesions	
		0-2	2-10	10-20	20-30	30-40	40-50	50+	Pos.	Neg.	Sinus Ear*	Primary	Pneumonia	Post-operative	Skull Frac.	None	Serum	Endocarditis	Brain Abscess
Finland ⁷	Cases	10	0	4	0	0	2	0	4	6	2	2	1	2	3	5	5	1	1
	Cures	6	0	3	3	0	0	0	0	6	1	1	0	1	3	3	3	0	0
	Per cent	60																	
Toomey ⁸	Cases	12	2	0	2	2	3	1	3	0	3	2	5	1	1	6	6	2	0
	Cures	5	0	0	2	1	1	0	1	0	2	1	1	1	0	2	3	0	0
	Per cent	42																	
Hodes ⁹	Cases	17	4	2	3	1	4	2	9	8	8	5	3	0	0	17	0	0	1
	Cures	8	0	1	2	0	3	2	4	4	4	3	1	0	0	8	0	0	0
	Per cent	47																	
Rhoads ¹⁰	Cases	22	1	3	6	1	3	5	13	5	6	9	5	0	2	5	17	3	1
	Cures	7	0	1	4	0	0	1	5	2	2	4	1	0	0	0	7	0	0
	Per cent	32																	
Neal ¹¹	Cases	30	5	5	3	4	2	8	10	10	20	7	0	0	3	9	21	0	2
	Cures	10	1	3	2	0	0	4	4	4	6	3	0	0	1	3	7	0	1
	Per cent	33																	
Vogelius ¹²	Cases	18	4	1	5	2	3	1	11	6	1	0	0	4	14	0	0
	Cures	4	0	0	3	1	0	0	2	2	0	0	0	1	3	0	0
	Per cent	22																	
Feldman ¹³	Cases	6	0	1	0	0	0	1	3	3	1	2	3	0	0	3	3	0	0
	Cures	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Per cent	0																	
Hartman ¹⁴	Cases	26	12	13	1	0	0	0	11	10	15*	3	7	1	0	14	12	0	3
	Cures	9	3	6	0	0	0	0	3	3	8	1	0	0	0	3	6	0	0
	Per cent	35																	
Sweet ¹⁵	Cases	40	6		8		26		4	15	15	0	2	19	21	4	0
	Cures	3	1		0		2		0	1	2	0	0	?	?	0	0
	Per cent	8																	
Totals	Cases	181	28	29	24	10	15	20	53	42	70	51	40	4	11	63	78	10	8
	Cures	52	4	14	16	2	4	7	17	19	25	16	5	2	4	20	29	0	1
	Per cent	29	14	48	67	20	27	35	32	45	36	31	13	50	36	32	37	0	13

* Entries in this column refer to ear or mastoid infection except for three cases of sinusitis with one recovery reported by Hartman.

be found and the survival rate was 31 per cent. However, when pneumonia was present, the prognosis was substantially altered for only 13 per cent were cured. The patients following skull fracture and operation on the cranial vault were too few in number to permit any conclusions. Plainly, the outlook in head injury is also greatly modified by such brain trauma as has occurred. Endocarditis was found post-mortem ten times but was not suspected in any patient who recovered. One brain abscess was diagnosed and successfully drained and seven others were found at autopsy.

who observed no recoveries, treated patients two-thirds of whom were over fifty and one-half of whom had pneumonia. The series of Sweet is unfavorably biased for the same reasons. Hence the alleged variation in the results obtained with the sulfonamides is more apparent than real and the recovery rate of about 30 per cent which is proposed in Tables II and III in all likelihood affords a reasonable estimate of what may be expected from these agents under ordinary circumstances.

Because of the great efficacy of newer drugs in the treatment of pneumococcal infections of all varieties, and also because

of the disappearance of commercial sources of type-specific antiserum, evaluation of antisera in the treatment of pneumococcal meningitis is no longer of practical concern. It is, however, a matter of historic interest and of some theoretic importance in the general therapy of bacterial disease. Certain clinical and experimental considerations in serotherapy of pneumococcal meningitis have been discussed by Finland.⁷ Briefly, in bacteremia accompanying lobar pneumonia organisms were often observed to proliferate in the circulating blood despite ordinarily adequate sulfanilamide treatment and sterilization occurred only after the establishment of a sufficiency of type-specific antibody, occurring either spontaneously or as a result of administration of antiserum. The continued multiplication of pneumococci was also observed to occur in the spinal fluid of certain patients while sulfanilamide was being administered and it was again found that sterilization might occur promptly when an antibody balance was established. Neither complement nor antibody, however, could be demonstrated regularly in the spinal fluid even when present in large amounts in the blood. This, of course, argued for the injection of type-specific antiserum into the subarachnoid space. Numerous observers were aware, however, that patients became worse in a manner quite different from any foreign protein reaction after intrathecal injection of serum. On the basis of test tube experiment, Finland found that large amounts of antiserum produced large aggregates of organisms and that phagocytosis was impaired mechanically and possibly by toxic action of the specific precipitate produced by the antigen-antibody combination on the granulocytes. He postulated further that this relatively massive agglutination might lead to subarachnoid block. On the basis of all these considerations it was suggested that the ideal in serotherapy might be production of antibody excess in the blood, artificially if necessary, and injection of only a small amount of antiserum into the intrathecal space. In certain instances

Finland injected the patient's own serum after it was demonstrated to be immune. This plan was used in some of his cases considered in Table III.

Table II contains information available regarding the value of serum as an adjuvant to sulfonamides. Steele and Gottlieb in their collected data found 57 per cent recoveries in patients treated by chemotherapy alone and 69 per cent in those who also received antiserum. They did not believe that this difference was significant. In subsequent reports (Table III) recovery rate without serum was 27 per cent, while on combined treatment 35 per cent survived. Adding these more recent results to those of Steele and Gottlieb the comparative rates are 41 and 42 per cent, respectively, and it seems clear that addition of antiserum was of no value. Quite different, however, was the conclusion of Hodes,¹⁷ who found that of thirty-two infants under age two (not all of whom could be included in Table III), six of eighteen treated with both agents recovered, while there was only one survival of fourteen patients treated with sulfonamide alone. In part D of Table II the available experience of others who have reported results in infants is added to that of Hodes and it is seen that only one cure was found among twenty-three patients treated by chemotherapy alone. The combination of serum and sulfonamide, employed in thirty-three babies, produced ten recoveries. The surviving group is not large enough to be divided on the basis of intrathecal and exclusively parathecal serotherapy. It is unfortunate that the serum question could not be examined in those infants in whom meningitis followed pneumonia; of recoveries in this situation, only three detailed descriptions could be found. It must be concluded, therefore, that the value of type-specific antiserum in sulfonamide-treated pneumococcal meningitis was never definitely determined. In infants serum-sulfonamide combinations produced strikingly better results than sulfonamide alone in the reported cases.

Since so many cases of pneumococcal meningitis arise from cranial suppuration, especially of the middle ear and mastoid bones, many clinicians believed that surgical attack on accessible infected foci was indicated in addition to chemotherapy. Opinion as to the value of drainage, however, was divided. Neal was of the opinion that "the importance of the eradication by surgery of foci of infection cannot be overestimated," while Hodes and his colleagues advocated postponement of such procedures until marked improvement had occurred, waiting if necessary as long as two or three weeks. They stated that "This delay in surgical intervention . . . contributed to recovery in a number of our patients." This question was most difficult to examine statistically. Aural paracentesis was almost always carried out in the patients in Table III when otitis was thought to be present and there appeared to be no reason to condemn so simple a maneuver. Of the seventy patients with ear, mastoid or sinus disease sixteen were subjected to more complicated surgery (usually mastoidectomy) and nine recovered, a survival rate of 56 per cent. Of fifty-four patients not operated upon, 30 per cent lived. In the series of Neal the recovery after drainage of a patient with a brain abscess has already been mentioned. These figures are not offered as conclusive because the value of any generalization is highly doubtful in a situation in which so many variables operate in each case.

The rapidity of clinical and bacteriologic response to sulfonamide treatment was very variable. In those patients who recovered and who had had frequent lumbar punctures, the spinal fluid was usually sterile between the fourth and seventh days of therapy. In a few instances negative cultures were obtained earlier and occasional subjects were encountered in which bacteria were isolated for many days, but eventual recovery occurred. Clinical improvement usually preceded or followed disappearance of organisms from the spinal fluid by about two days.

Relapse was an event which occurred

quite regularly with sulfonamide treatment of meningitis due to the pneumococcus. Coleman⁶ found this accident six times among twenty-nine patients; at least ten other patients have been described, including several with multiple recurrences.²¹⁻²⁸ In the early days of sulfonamide chemotherapy it was common practice to reduce dosage of the drug as soon as a definite response occurred and this procedure was associated with most of the relapses which occurred before treatment had been discontinued. Renewed evidence of meningeal infection sometimes appeared as long as a month after cure had apparently been effected. Multiple recurrences were occasionally terminated by discovery and eradication of a previously unsuspected focus of infection; more often these searches were fruitless. In the material which appears in Table III, eight relapses were mentioned. This may not represent the true incidence since protocols were not always given in the fatal cases. Both of the patients observed by Neal and her group occurred about two weeks after apparently satisfactory therapy. One died; the other was successfully retreated. Hartman gives details of two patients who recovered after relapse associated with reduction in sulfonamide medication and one who was finally cured after an unexplained recurrence under full therapy. One of his cases relapsed after a month of observation and responded satisfactorily to re-treatment. Two patients showed transitory clinical and bacteriologic improvement and then died.

Complications following recovery from this disease have not been adequately described and information in regard to adults is especially deficient. Keefer¹ described arachnoiditis in his patient. In Finland's series deafness appeared early in one patient and was persistent. The patient whose disease followed partial removal of a brain tumor left the hospital with ataxia. Hodes mentioned slight weakness of one hand in a single patient. Hartman followed his group of infants and children especially carefully for the appearance of neurologic

residua. His studies included psychometric examinations and a number of serial encephalograms. He concluded that all young children during pneumococcal meningitis develop radiographically demonstrable hydrocephalus which may be transitory and without permanent effect. One of his patients, however, had persistence of this disorder associated with progressive mental deterioration. A second patient had convulsions and marked intellectual deficiency after two and one-half years. There were two children partly or totally deaf after more than six months and one with hemiparesis. Thus, severe and permanent neurologic damage occurred in five of Hartman's nine recoveries.

In summary, it may be said that recovery rate in pneumococcal meningitis treated with the sulfonamides is about 30 per cent and is influenced markedly by the patient's age and the source of the infection. The value of type-specific serotherapy as an adjuvant has never been properly assessed, but it appears to improve the results obtained in the treatment of infants. Also not evaluated, and possibly incapable of statistical evaluation, is surgical drainage of foci of infection which are commonly present. Relapse following sulfonamide therapy occurs regularly although not apparently with great frequency and is not necessarily associated with eventual fatality. Permanent neurologic damage has not been frequently reported in adults; in young children it is common and often severe.

In 1942 penicillin became available in small amounts and its value in the treatment of infections due to the pneumococcus soon became apparent. By August, 1943, the Committee on Chemotherapeutics of the National Research Council released a report describing the results obtained with the new drug in 500 subjects with various infections, including twenty-three patients with pneumococcal meningitis.²⁹ Only seven recoveries were noted, but the Committee remarked that the dosages were small and that not all of the patients had received intrathecal penicillin.

Table iv contains a partial analysis of 119 patients with pneumococcal meningitis treated with penicillin without the simultaneous administration of a sulfonamide. Most of these histories have also been collected by Walker and Johnson.⁴² Only twenty-two of these patients could be analyzed in detail because of those reported by Appelbaum³² and by White,³³ a total of twenty received simultaneous sulfonamide chemotherapy. These have been deducted from "totals," given in the first column of Table iv but could not be identified or removed from the analysis by age and focus of infection. These data are given in order to show the composition of the authors' groups, but they cannot be added to those known to have been treated without other agents. Eight reports of patients with sinusitis and ear and mastoid infections are tabulated.

Almost all of these patients had received sulfonamide in varying amounts prior to administration of penicillin. However, in over one-half of the group it was stated by the author that organisms were still present in the spinal fluid often in numbers large enough to permit direct typing. Two of the patients of Harford³¹ were given courses of sulfonamide to diminish the likelihood of relapse after clinical and bacteriologic cure had been obtained with penicillin. Seven of the patients reported by White and his colleagues received no intrathecal penicillin and of these three recovered. The adults of White's group usually received between 50,000 and 100,000 units daily by intramuscular or intravenous injection. Two of Appelbaum's patients received exclusively intrathecal therapy.* With these exceptions, all other patients were treated with reasonable amounts of penicillin intramuscularly (or intravenously) and intrathecally. Most adults were given 20,000 to 30,000 units at least every three hours intramuscularly and from 10,000 to 20,000

* Cairns and his co-workers have reported four recoveries among eight patients in whom the only treatment consisted of introduction of penicillin into the cerebral ventricles or lumbar sac.³⁷

units intrathecally once or twice daily. In addition to the intraspinal route injections were sometimes made into the basal cistern and occasionally into the ventricles. The doses of penicillin were limited by the early scarcity of the drug and often were not optimal by current standards. More-

nearly the same. Of ten infants treated with penicillin alone there were six recoveries. This number is too small to compare directly with the 14 per cent survival rate found with sulfonamides for this age group but suggests an improvement in results, as does the small series of patients over fifty.

TABLE IV

ANALYSIS OF CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH PENICILLIN WITHOUT SULFONAMIDES WAS USED

Author	Totals	Age Group in Years							Blood Culture		Pathogenesis of Meningitis				Other Rx		Additional Lesions	
		0-2	2-10	10-20	20-30	30-40	40-50	50+	Pos.	Neg.	Sinus Ear*	Pri- mary	Pneu- monia	Skull Frac.	None	Serum	Endo- cardi- tis	Brain Abs- cess
Sweet ¹³	Cases	3	0	0	0	0	0	1	2	1	1	1	0	3	0	0
	Cures	1	0	0	0	0	0	1	0	1	0	0	0	1	0	0
	Per cent	33																
Hartman ¹⁴	Cases	3	2	1	0	0	0	0	0	0	3	1	2	0	0	1	2	0
	Cures	1	1	0	0	0	0	0	0	0	1	1	0	0	0	1	0	0
	Per cent	33																
Hutchins ²⁰	Cases	7	7	0	0	0	0	0	0	0	7	0	0
	Cures	5	5	0	0	0	0	0	0	0	5	0	0
	Per cent	72																
Harford ²¹	Cases	9	1	0	3	0	0	2	3	6	3	4	3	2	0	9	0	0
	Cures	8	0	0	3	0	0	2	3	6	2	4	3	1	0	8	0	0
	Per cent	89																
Totals.....	Cases	22	10	1	3	0	0	3	5	6	6	6	6	3	0	20	2	0
	Cures	15	6	0	3	0	0	3	3	6	3	6	3	1	0	15	0	0
	Per cent	68	60	0	100	0	0	100	60	100	50	100	50	33	0	75	0	0
Appelbaum ²²	Cases	54	(0-1)	(1-10)														
	Cures	20	11	6	2	1	7	12	28	33	16	32*	16	17	2	50	4	0
	Per cent	37	4	5	1	1	4	3	8	?	?	15	4	5	2	?	?	0
White ²²	Cases	43	(0-2)	(2-15)	(16-30)	(31-50)												
	Cures	15	12	9	6	12	17	23	18	29*	12	9	40	3	4	3
	Per cent	34	5	4	0	7	2	8	8	8	6	4	14	1	0	0
Totals.....	Cases	119																
	Cures	50																
	Per cent	42																

* Entries in this column refer to ear or mastoid infection except for eight cases of sinusitis. Of these two with no recoveries were reported by Appelbaum and six with one recovery by White.

over, the reported data are not ideal for purposes of analysis. Table iv represents, however, the available information on the efficacy of penicillin without simultaneous sulfonamide. Eleven of this group also received specific antiserum and it is known that of these six died. Thus, it is safe to state that mortality in the total group was not reduced by the use of serum. Of the 119 patients fifty or 42 per cent survived. It should be noted that Table iv includes relatively more than twice as many patients under age two and past age fifty as does the sulfonamide series of Table iii; the incidence of pneumonia, however, is

In Table v appears an analysis of the reported patients treated simultaneously with penicillin and a sulfonamide and appended are the twenty subjects of White and of Appelbaum previously referred to. The overall recovery rate was 62 per cent which is twice that found with sulfonamide alone. In the sixty-six detailed reports it may be seen that there are few aged patients compared to those in the group treated by other methods. This is more than outweighed by the fact that of the sixty-six penicillin-sulfonamide treated patients, almost half were infants under age two and that 81 per cent recoveries were obtained

in this age group in which the outlook has always been so poor. An insufficient number of patients with meningitis consequent on pneumonia were treated by this plan to make any comparison.

An effort was made to present separately the results obtained with penicillin alone

those treated with penicillin, with or without sulfonamide. The results in patients who received penicillin are five times better in infants, over twice as good in the elderly and three and one-half times better in patients with pneumonia.

Results obtained in the treatment of

TABLE V

ANALYSIS OF CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH PENICILLIN AND SULFONAMIDE WERE USED

Author		Totals	Age Group in Years							Blood Culture		Pathogenesis of Meningitis				Other Rx		Additional Lesions	
			0-2	2-10	10-20	20-30	30-40	40-50	50+	Pos.	Neg.	Ear	Primary	Pneumonia	Skull Frac.	None	Serum	Endocarditis	Brain Abscess
A. J. Waring ²⁴	Cases	12	8	1	0	0	0	1	2	7	0	6	1	3	0	9	3	0	0
	Cures	11	7	1	0	0	0	1	2	?	0	6	1	3	0	8	3	0	0
	Per cent	92																	
Sweet ¹⁵	Cases	13	2	0	1	1	1	6	2	1	7	3	1	11	2	1	0
	Cures	6	2	0	1	1	1	1	0	1	3	1	1	4	2	0	0
	Per cent	96																	
Hartman ¹⁴	Cases	5	5	0	0	0	0	0	0	2	2	4	1	0	0	2	3	0	0
	Cures	3	3	0	0	0	0	0	0	2	1	3	0	0	0	1	2	0	0
	Per cent	60																	
Hutchins ³⁰	Cases	7	7	0	0	0	0	0	0	3	4	0	0
	Cures	4	4	0	0	0	0	0	0	2	2	0	0
	Per cent	57																	
Ross ²⁸	Cases	19	14	4	1	0	0	0	0	0	12	7	0	0
	Cures	16	13	3	0	0	0	0	0	0	10	6	0	0
	Per cent	84																	
Jepson ²⁶	Cases	10	All in Military Age Group							0	0	0	10	10	0	0	0
	Cures	5								0	0	0	5	5	0	0	0
	Per cent	50																	
Totals	Cases	66	36	5	2	1	1	7	4	2	2	11	9	6	11	47	19	1	0
	Cures	45	29	4	1	1	1	2	2	2	1	10	4	4	6	30	15	0	0
	Per cent	64	81	80	50	100	100	28	50	100	50	91	45	67	55	64	79	0	0
Appelbaum ²²	Cases	13																	
	Cures	5																	
	Per cent	38																	
White ²³	Cases	7																	
	Cures	3																	
	Per cent	43																	
Total	Cases	86																	
	Cures	53																	
	Per cent	62																	

and those observed with adjuvant sulfonamide. Analysis suggests but does not prove that combined therapy is of greater value. It is unfortunate that of the cases treated with both agents, half of those suitable for detailed analysis also received type-specific antiserum. The results with and without this third drug were the same but comparison is further complicated.

In order to show clearly the great value of penicillin in meningitis due to the pneumococcus, the final section of Table II shows the results reported separately in infants, in the aged, in patients with pneumonia treated with sulfonamide and in

pneumococcus meningitis at the Evans and Haynes Memorials are shown in Table VI. When penicillin became available, nine patients were treated with this agent alone and only one recovered. In view of the results obtained subsequently with combined therapy, an impression was formed as to the advantages of simultaneous sulfonamide administration which, in retrospect, is probably not justifiable. Examination of the discouraging cases in part A of Table VI shows that six of the nine patients were either infants or aged (three in fact were past sixty-five), and a formidable group of complications was encountered

including a brain abscess and a case of ulcerative endocarditis. One of the two patients in the less unfavorable age group had a major congenital heart lesion with marked cyanosis (without postmortem evidence of endocarditis). Of eighteen patients

of their patients organisms could not be recovered twelve to twenty-four hours after treatment was begun. The fluid in fifty-three of Appelbaum's sixty-seven patients was sterile after forty-eight hours³² and Hartman¹⁴ obtained negative cultures from

TABLE VI
ANALYSIS OF EVANS AND HAYNES MEMORIAL CASES OF PNEUMOCOCCAL MENINGITIS IN WHICH PENICILLIN WAS USED

Totals		Age Group, Years							Blood Culture		Pathogenesis of Meningitis					Other Rx		Additional Lesions		
		0-2	2-10	10-20	20-30	30-40	40-50	50+	Pos.	Neg.	Ear	Sinus	Primary	Pneumonia	Skull Frac.	None	Serum			
A.	Cases	9	1	0	1	0	1	1	5	9	0	2	2	3	2	0	9	0	Brain abscess	1
	Cures	1	0	0	0	0	0	0	1	1	0	0	0	1	0	0	1	0	Pericarditis	1
	Per cent	11																	Congenital heart	1
																			Vascular accident	1
																			Endocarditis	1
B.	Cases	18	0	1	3	2	3	2	7	9	9	3	4	6	4	1	17	1	Endocarditis	?2
	Cures	15	0	1	3	2	2	1	6	7	8	2	3	6	3	1	15	0	Previous recovery	1
	Per cent	83																	Diabetes	1

A. Patients treated with penicillin without simultaneous sulfonamide.

B. Patients treated with penicillin and sulfonamide.

treated with both penicillin and sulfonamide, there were fifteen recoveries (78 per cent). Although there were no infants in this series, seven of the group were over fifty years old and three of the four patients with pneumonia were in the sixth decade of life. Hence, it is not believed that this material is unduly biased by favorable statistical selection. However, these results are neither suitable for comparison with those reported in the treatment of infants nor should they be compared strictly with those obtained in this clinic with penicillin alone. This latter reservation may possibly apply also to the report of Smith and his colleagues³⁸ who obtained 63 per cent recoveries without the use of sulfonamide and 90 per cent with combined treatment. Their paper described nineteen cases in each group but did not present the details of individual patients.

In general, sterilization of the spinal fluid appeared to occur more promptly in penicillin-treated patients than in those of the sulfonamide series. Waring and Smith³⁴ gave four days as the average time in their cases and they found that in over one-half

most of his patients on the second day. Relapse, however, was encountered regularly and was definitely mentioned eighteen times in the collected cases, which suggests that this difficulty was at least as frequent with penicillin as with sulfonamide. It was seen in one of the twenty-seven patients at this clinic but recovery ensued after three recurrences all during treatment. More often, however, relapses developed soon after therapy was discontinued. Neurologic complications appearing during or after treatment of pneumococcal meningitis are of especial interest and importance since some clinicians believe that certain of these changes result from the subarachnoid injection of penicillin rather than from the disease itself. This possibility is discussed in a subsequent section.

A two month old infant treated by Waring and Smith³⁴ made a prompt bacteriologic and clinical response but developed optic atrophy and blindness. This patient received an intrathecal injection of 20,000 units of penicillin. In view of this dose, relatively large for an infant, and the otherwise favorable course of the infection, it was

suggested that the medication rather than the meningitis may have caused this complication. Sweet and his colleagues¹⁵ encountered two mild and two severe cases of myelopathy about whom they raised this question.

Aside from their case of blindness Waring and Smith reported one patient who became deaf and one with spastic monoplegia. In White's series³³ three young children were spastic but were said to be improving. One patient whose age was not given developed a "mental disturbance" and died three and one-half months after his meningitis was healed. Ross³⁵ encountered a case of deafness and one of spasticity and blindness. Hutchins³⁰ reported persistent hydrocephalus once, "motor retardation" once and four patients with severe cerebral damage, one of whom died two months later presumably of this cause. One example of hemiparesis, one of deafness and one of severe hydrocephalus were described by Hartman.¹⁴ Two of the fatalities in his series were shown to have made a bacteriologic recovery but died during or shortly after treatment, probably from brain damage. Thus of 103 patients who survived therapy consisting wholly or in part of penicillin, significant central nervous system residuals were mentioned in twenty-three.

Brain abscess was present in five of the published cases and was found once among the group of the Evans and Haynes Memorials. None of these patients survived. There was autopsy proof or convincing clinical evidence of ulcerative endocarditis in six of the cases here reviewed and in three of the observed series. Since no report of recovery from pneumococcus meningitis complicated by endocarditis has been encountered, 2 patients in whom this combination appeared probable are briefly described. Both were treated with penicillin and sulfonamide.

CASE REPORTS

CASE I. A forty-nine year old man developed pneumococcus meningitis while supposedly convalescing from his third attack of pneumonia

in six months. Bacteremia was demonstrated. He responded well to treatment but in the third week in the hospital a loud aortic diastolic murmur was heard for the first time. Congestive failure developed rapidly and was controlled only intermittently by digitalis. He died of cardiac decompensation thirteen months later. Permission for autopsy was denied.

CASE II. A thirty-eight year old woman, believed to be an alcoholic, developed pneumococcus meningitis with bacteremia after a prolonged respiratory infection of uncertain type. An aortic diastolic murmur was first discovered the day following admission. Infection was promptly controlled and no cardiac symptoms appeared although tachycardia and a gallop rhythm were repeatedly found and digitalis was given. Two months later she had no complaints and was then lost from observation. She died of pneumonia in another hospital after about six months and it was stated that a clean perforation was found in one of the aortic cusps at postmortem.

An unusual patient in the Haynes material was a young male who recovered from meningitis due to pneumococcus type 24. Six years before he had sustained a head injury and had been successfully treated with sulfanilamide and sulfapyridine for pneumococcus meningitis, type 6. This patient is most interesting in light of the observations of Linell and Robinson,² already mentioned.

Briefly, it may be concluded that penicillin has significantly improved the recovery rate in pneumococcal meningitis. Statistical proof of the efficacy of penicillin rests especially upon results obtained in young children and is most striking when adjuvant sulfonamide chemotherapy is used. The overall value of this combined therapy cannot be rigidly determined but the gross recovery rate appears to be somewhat higher (Tables iv and v) when both agents are used. Serious prolonged or permanent neurologic complications were described in about 20 per cent of the penicillin-treated cases. The spinal fluid is usually sterilized more promptly with penicillin than with sulfonamides. Tendency to relapse appears to be about the same as with

the latter agent. On the basis of the information available it is not possible to estimate the value of surgical treatment of demonstrable foci of infection in penicillin-treated cases.

As experience with penicillin treatment of bacterial meningitis has accumulated several authors have suggested that introduction of this agent directly into the subarachnoid system is unnecessary, and others urge that under certain circumstances it may even be dangerous.

It is generally accepted that in normal persons penicillin does not appear in the spinal fluid in significant amounts after intravenous or intramuscular injection of ordinary or even large doses.^{39,46} While Rosenberg and Sylvester⁴⁰ have shown that therapeutic levels are present in the spinal fluids of patients with meningitis up to 140 minutes after parathecal administration, the studies of Ross³⁵ and of Cooke and Goldring⁴¹ clearly show that effective amounts of penicillin do not cross the blood brain barrier in all or even in the majority of cases despite the presence of meningeal inflammation. Walker and Johnson⁴² agree that systemic injections cannot be depended upon to produce optimal levels in the cerebrospinal fluid. However, because intrathecal penicillin is occasionally followed by nervous system damage, the whole concept of topical therapy to the meninges has been questioned on the ground that the antibacterial agent in the circulating blood may be adequate to sterilize these tissues without re-enforcement from the spinal fluid. While this possibility cannot be denied, it has not been established in pneumococcal meningitis by reports of isolated cures obtained exclusively by systemic therapy.^{29,33,43} Since penicillin is known to be highly effective against the pneumococcus, it is not surprising that a certain number of recoveries occur with treatment programs of less than maximal intensity. However, it was pointed out earlier in this discussion that the reported overall mortality of patients with penicillin-treated pneumococcal meningitis is still 40 per

cent; thus, any reduction in therapeutic effort based only on theoretic reasoning seems unjustified.

A more difficult problem is posed by observations which suggest that introduction of penicillin directly into the nervous system is not a safe procedure under all conditions. Headache and pleocytosis in the spinal fluid were encountered in the early pharmacologic studies³⁹ of the drug but it has never been shown that these changes are important. Of interest but of uncertain significance is the simultaneous appearance of urticaria and the neurologic findings of peripheral neuritis in a patient under therapy for a joint space infection who received no intrathecal penicillin.⁴⁴ The more alarming manifestations associated with subarachnoid administration of this agent are of two types: (1) cortical irritation resulting in convulsions and (2) hypertrophy of the leptomeninges, sometimes causing radiculopathy and myelopathy.

Johnson and Walker⁴² discussed the case of a baby in whom meningitis developed after a catheter was introduced into a cerebral ventricle to effect decompression. The infection was almost symptomless but when 50,000 units of penicillin in 5 cc. of normal saline were injected into the catheter, circulatory collapse and severe convulsions occurred which, however, were followed by spectacular improvement within a few hours. Milder seizures followed doses of 15,000 units in this patient and his infection was eventually cured. These investigators were able to produce fits regularly in cats and monkeys by superficial injections into the cortex and found the effect to be proportional to the amount of penicillin introduced and to occur with highly purified or crystalline preparations. When deactivation of the drug was accomplished by physical and chemical manipulations, the decrease in antibacterial potency was found to be fairly closely correlated with diminished irritative activity. Pilcher, Meacham and Smith⁴⁵ produced convulsions in dogs by cortical injections and also by cisternal and ventricular administration.

They emphasized that the convulsant dose for a 10 Kg. dog by the cisternal route is equivalent to over 50,000 units for a 70 Kg. human and interpreted their findings to mean only that excessive medication should be avoided.

Seizures in humans due to spinal or cisternal injection of penicillin have not been frequently observed but there are additional reports describing such episodes in patients who received excessive doses^{46,47} although large amounts have been tolerated in other cases.³⁷ It is possible that over-medication accounted for persistent lateralized twitchings in a young infant treated with intrathecal penicillin for meningococcal meningitis at the Haynes Memorial although these episodes (as did some of those reported) occurred before the disease was fully controlled. Experimental and clinical evidence clearly shows that convulsions result when high penicillin levels are produced in the excitable areas of the nervous system, a situation which can be avoided when less massive doses are employed and injections are made only into the lumbar sac or basal cistern. The view that penicillin produces inflammation of the leptomeninges beyond that resulting from the infection is more difficult to assess. Reference has already been made to the appearance of symptoms of cord and root disorder in several patients treated with intrathecal injection. Walker⁴⁸ and Walker and Johnson⁴² have described three additional cases and three other reports of single cases have appeared, one of these a patient with meningococcal meningitis.⁴⁹⁻⁵¹ Two patients were subjected to exploratory laminectomy and marked proliferation of the arachnoid was found.^{48,49} Experimentally injected normal monkeys were said to behave as if experiencing caudal paresthesia and to show at autopsy the previously described meningeal changes.⁴²

Among patients treated at the Evans and Haynes Memorials complaints of root pain have been encountered with great frequency and occurred at the time injection was actually being made, disappearing

within a few minutes. With the exception of one patient with foot drop, no persistent or permanent neurological residuals of root type have been seen and disability in this patient was believed at the time to have resulted from accidental injection of the sciatic nerve during simultaneous intramuscular administration.

On the basis of existing information it is not possible to separate clearly certain lesions possibly caused by therapy from those due to the violent leptomeningitis known to be produced by the pneumococcus. Some of the evidence incriminating penicillin as a cause of root and cord damage is quite suggestive and for the time being it seems necessary to view the development of such reactions as a possible hazard of intrathecal treatment; since excessive doses were not employed in all the recorded cases, it is one which is not readily preventable. Nevertheless, it is believed in this clinic that the risk of such an accident is preferable to any compromise in antibacterial therapy and it is, therefore, present practice to administer intrathecal penicillin to adults in amounts between 25,000 and 50,000 units and in volumes of at least 10 cc. of normal saline or spinal fluid. For infants and children the dose is reduced approximately in proportion to weight. The first two or three injections are sometimes given at twelve-hour intervals; otherwise they are made once daily. Walker and Johnson concluded, on the basis of their own and observations of others, that there is marked individual variation in the persistence of desirable spinal fluid levels after introduction of penicillin into either the spinal or cisternal spaces⁴² and treatments at twelve-hour intervals may be indicated for several days in some cases. No sites of subarachnoid injection other than the lumbar sac and, on occasion, the basal cistern are employed. While cisternal treatment has not been routinely practiced, there is evidence that much better diffusion of penicillin into the cerebral ventricles occurs after cisternal than after lumbar administration.⁴² Treat-

ment is usually continued for a minimum of ten days and is prolonged without hesitation if indications arise.

SUMMARY AND CONCLUSIONS

1. A number of features of the natural history of pneumococcus meningitis have been discussed. Prominent among these are the facts that about 40 per cent of cases arise from infection of the middle ear and about 25 per cent from pneumonia. The disease is common in infants and also occurs in the aged. Previous to the introduction of the sulfonamides almost all cases resulted fatally.

2. With appropriate treatment a substantial number of patients can be saved. The results in infants, the aged and in cases following pneumonia are distinctly less favorable, and it is of greatest importance to apply these facts in comparing the results of various clinics and of different therapeutic programs. With these limitations in mind, it is suggested that 30 per cent is a reasonable estimate of the recovery rate which may be expected from sulfonamide treatment. Similarly, 60 to 70 per cent is proposed for the penicillin survival rate, this figure including those patients who receive sulfonamides in addition. In adult patients treated early in the course of the disease it is possible that even better results may be obtained.

3. Penicillin is without question the agent of choice in the management of this disease. Systemic and topical administration is recommended. While there is suggestive evidence that subarachnoid injection of this drug may cause occasional reaction, untoward effects are not common if excessive dosage is avoided and the theoretic advantage of maintaining effective penicillin levels in the spinal fluid is great. This cannot be accomplished with certainty by exclusively systemic therapy. Simultaneous administration of sulfonamide is advised although rigid statistical proof of added effect is not available.

4. Neural complications are rather common especially in infants. Brain abscess and

endocarditis are not common, but when present greatly reduce the chance of survival, although two patients recovered in this clinic despite probable endocarditis. These cases are briefly described.

5. An outline of the specific therapeutic principles employed at the Evans and Haynes Memorials follows:

(1) Establishment of bacteriologic diagnosis as rapidly as possible.

(2) Intramuscular penicillin, 40,000 units every three hours.

(3) Intrathecal penicillin injected into the lumbar sac in an amount not greater than 50,000 units for adults in a volume of at least 5 cc. of normal saline or spinal fluid. In patients weighing under 90 pounds dosage is reduced approximately by a factor equal to the weight divided by 100. In seriously ill patients the first two or three treatments are given at intervals of twelve hours, thereafter every twenty-four hours. If block is suspected or if free flow of fluid from the lumbar space becomes unobtainable, cisternal injections are made.

(4) Adequate hydration is urged. This may be accomplished by whatever means are necessary, as judged by the formation of moderately dilute urine during the first few hours in the hospital. Hydration should be followed by administration of sulfadiazine in amounts sufficient to produce a blood concentration of about 15 mg. per cent free drug. This has seemed to be easier with sulfadiazine than other compounds of the sulfonamide group. The urine is examined daily or more often.

(5) Necessary mechanical expedients to accomplish these ends in combative or comatose patients are physical restraint with soft flannel bandages, paraldehyde sedation freely but only when necessary and the use of the retention catheter.

6. Full therapy is usually continued for eight to ten days after the spinal fluid is sterile. If there is bacteriologic or other laboratory and clinical evidence of recovery of all known sites of infection, intrathecal penicillin is omitted. If progress is favorable, intramuscular penicillin is elimi-

nated during the next two or three days and sulfadiazine stopped before the end of that week.

5. The problem of surgical attack on infected foci has not been frequently encountered. It is tentatively believed that such intervention should be delayed until marked improvement has occurred or demonstrated to be highly unlikely as the result of antibiotic therapy.

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Seminars on Protein Hydrolysates

Utilization of Protein Hydrolysates by Normal and Protein-Depleted Animals*

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AMINO acids, arranged in various patterns into proteins, form the matrix of the living system; they are the catalysts, the centers around which the dynamic equilibria of life develop. Growth, maintenance and the well being of the living system are functions of the reproduction of these patterns, the formation of which are dependent upon a proper distribution and utilization of raw materials in the diet. The most fundamental of these raw materials are the so-called essential amino acids. They are the amino acids which cannot be manufactured by the animal body in sufficient quantities to meet its demands and must, therefore, be supplied in the diet.

Modern research on the nutritive rôle of amino acids began when mixtures of purified amino acids replaced proteins in the diet of animals, research which was inaugurated by Rose¹ at the University of Illinois in 1930. From these studies it was discovered that a mixture of ten of the amino acids, namely, valine, methionine, threonine, leucine, isoleucine, phenylalanine, tryptophane, lysine, histidine and arginine are essential for the growth of the rat. Recently Rose² has demonstrated that except for histidine and arginine these same amino acids are essential for the maintenance of nitrogen equilibrium in man.

NITROGEN EQUILIBRIUM

A study involving the measurement of nitrogen equilibrium is one of the most simple approaches to evaluation of amino acids or their derivatives in the living system. An animal is said to be in nitrogen equilibrium when the nitrogen intake is equal to the nitrogen excreted, a condition in which the nitrogen integrity of the animal is just being maintained. If one of the essential amino acids is eliminated from the diet, the animal cannot be maintained in nitrogen equilibrium but will excrete more nitrogen than is taken into the body. There are no body reserves of essential amino acids which can be drawn upon to supplement an inadequate pattern of dietary amino acids. The amount of dietary nitrogen necessary to maintain equilibrium increases, therefore, as the concentration of essential amino acids in the foodstuff decreases, becoming infinite if an essential amino acid is entirely absent. An acid hydrolysate of casein in which the tryptophane was destroyed by the acid would not, for example, maintain nitrogen equilibrium in a dog. When an optimum amount of this essential amino acid was added to the hydrolysate, the dog was maintained in nitrogen equilibrium by intravenous feedings of 300 mg. of nitrogen/day/Kg. of body weight. When insufficient tryptophane was

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added, 700 mg./day/Kg. of this same hydrolysate was fed intravenously to maintain nitrogen equilibrium. The minimum amount of nitrogen necessary to maintain nitrogen equilibrium is used, therefore, as a method of evaluating amino acids, protein

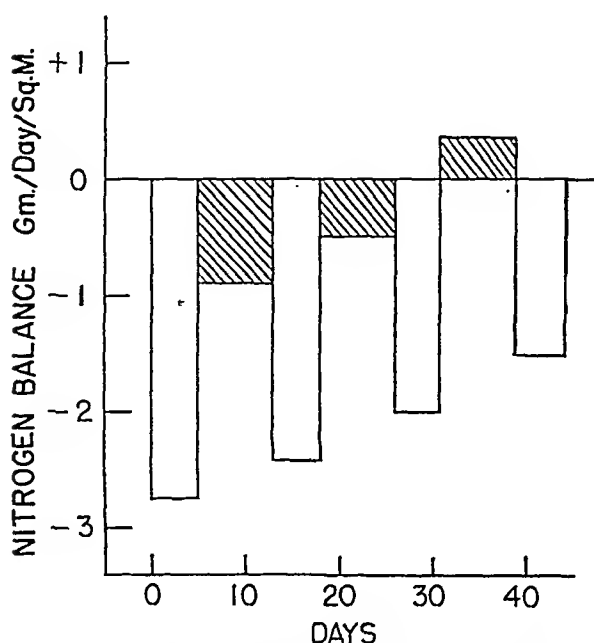


FIG. 1. Average nitrogen balances produced in three dogs fed a protein-free diet (white bars) and a diet containing a 3.60 Gm. wheat gluten nitrogen/day/sq. M. body surface area (bars with slanted lines).

hydrolysates and proteins in animals and in man. The objection to this method of evaluation is the variation in minima which is associated with changing protein stores.

The protein stores of the animal are the labile cytoplasmic proteins found in the liver, plasma and muscle tissues of the body. There are no protein reserves in the same sense that there are fat or carbohydrate reserves but the body can and does utilize cellular proteins to maintain the nitrogen integrity of essential tissues. When an animal is fed a protein-free diet, nitrogen is excreted in the urine, nitrogen which comes from the catabolism of tissue proteins. The amount of nitrogen excreted when the animal is eating a protein-free diet is a measure of the magnitude of the protein stores of the body, being high when the labile cytoplasmic proteins are in abundance and being low when these stores are de-

pleted. Much less dietary nitrogen is needed to maintain the *status quo* of tissues in a protein-depleted animal than in one in which the tissues have grown in nitrogen to the fullest extent.

The relationship between nitrogen excretion and the protein stores of the animal are illustrated in Figure 1 in which the nitrogen balance is plotted against time in days. These are average data obtained on three dogs which were fed a protein-free diet for the first five days during which time they excreted 2.75 Gm. of nitrogen/day/sq. M. of body surface area (first white bar). Then the dogs received a constant protein intake of wheat gluten for eight days. During this period the nitrogen excretion was greater than the intake giving a negative nitrogen balance of 0.9 Gm./day/sq. M. (bar with slanted lines). The protein-free diet was substituted for wheat gluten for the next five days and the nitrogen excretion became 2.25 Gm./day/sq. M. In this way the dogs were fed alternately protein-free and the wheat gluten diet. The continued loss of tissue nitrogen while in negative nitrogen balance caused a gradual decrease in excretion of nitrogen so that after thirty days the wheat gluten diet was sufficient to put the dogs in positive nitrogen balance. Thus, the dogs went from a condition in which they lost nitrogen to one in which they gained nitrogen during the period of feeding of a constant quantity of protein. At the end of thirty days the dogs were so depleted in protein stores that much less dietary nitrogen was needed to maintain nitrogen equilibrium than at the beginning of the experiment.

Further effects of reducing the protein stores on nitrogen balance are illustrated in Figure 2. The data plotted in this figure illustrate results obtained while feeding a good source of nitrogen, such as egg proteins. This figure demonstrates that the relationship between absorbed nitrogen and nitrogen balance is linear in the region of negative nitrogen balance, the linearity extending over into positive balance be-

coming eventually curvilinear in this region. The linear relationship is defined by the following equation: $NB = K (AN) - N_{EO}$ when NB is nitrogen balance, K is the slope of the line, (AN) is absorbed nitrogen and N_{EO} is the excretion of nitrogen on a protein-free diet, the Y intercept of the line.³ As the excretion of body nitrogen decreases the amount of nitrogen necessary to maintain nitrogen equilibrium decreases. When the excretion of nitrogen on a protein-free diet (N_{EO}), for example, is 3 Gm./day/sq. M., approximately 3.2 Gm./day/sq. M. of absorbed nitrogen are necessary to maintain nitrogen equilibrium, but when it is 1.3 Gm./day/sq. M. only 1.1 Gm./day/sq. M. are required.

Nitrogen Balance Indexes in Oral Feeding. The slope (K) of the lines in Figure 2 represent the rate of change of nitrogen balance with respect to absorbed nitrogen which is the rate at which a nitrogen source will establish equilibrium in an animal. For that reason this slope has been called the nitrogen balance index of the protein source.⁴ Curve A represents data obtained on a normal dog while B illustrates the relationship found in a depleted animal. The nitrogen balance index is constant and independent of the protein stores in the normal dog but becomes a variable increasing in magnitude in the protein-depleted animal. The average index of the sample of egg protein illustrated by the data in this figure is 0.9 in normal dogs and is 1.0 in the depleted dog. The difference between the index in the normal and depleted animal becomes greater as the index decreases in value. The index for wheat gluten, for example, in the normal dog is 0.45 while in the depleted animal it is 0.7. The pattern of amino acids is retained better in the depleted than in the normal dog.⁵

As the protein stores decrease, reflected by a decrease in excretion of nitrogen on the protein-free diet (N_{EO}), the curves extend further and further into the region of positive nitrogen balance. Thus, the possibilities for growth in nitrogen become

greater and greater as the animal is depleted in proteins. Indeed, the degree of depletion can be estimated by the magnitude of positive nitrogen balance which can be produced in the animal.

Some nitrogen balance indexes obtained

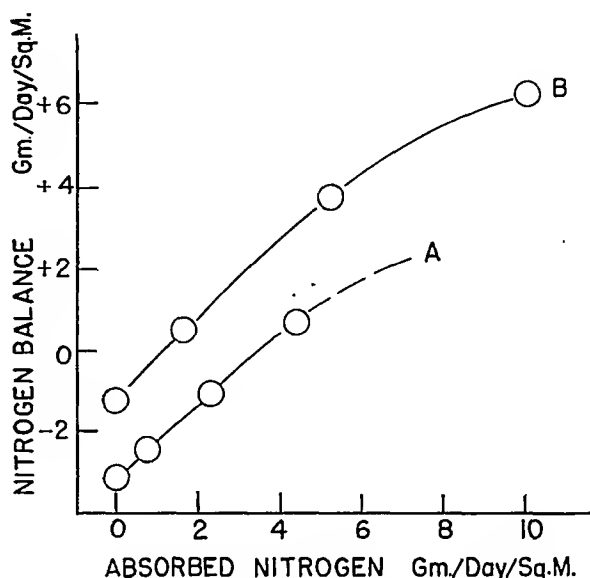


FIG. 2. Average nitrogen balances produced while feeding different amounts of whole egg nitrogen to three normal dogs (A) and three protein-depleted dogs (B). The data are expressed as Gm./day/sq. M of body surface area.

by oral feeding of various nitrogen sources to normal dogs are recorded in Table I. The indexes vary from over unity for the best nitrogen sources to 0.4 for the poorest. More nitrogen is required, therefore, to maintain nitrogen equilibrium with wheat

TABLE I*
NITROGEN SOURCES AND NITROGEN BALANCE INDEXES IN NORMAL DOGS

Nitrogen Source	Nitrogen Balance Index K
Cascin + methionine.....	1.2
Egg white.....	1.0
Lactalbumin.....	1.0
Lactalbumin hydrolysate.....	1.0
Bovine muscle meat.....	0.85
Casein.....	0.80
Cascin hydrolysate.....	0.80
Wheat gluten + lysine.....	0.82
Chicken entrails.....	0.77
Flounder heads.....	0.55
Wheat gluten.....	0.44
α Protein.....	0.39

* Some of these data were taken from a paper by Allison, Anderson and Seeley.⁴

gluten than with egg white or whole egg proteins. The increase in the index of wheat gluten from 0.44 to 0.82 when lysine is added reflects an improvement in the amino acid pattern.⁶ Similarly, casein is improved by adding methionine. Both the dog⁷ and the rat^{8,9} tend to be short on methionine so that addition of an optimum quantity of this amino acid to their diets often improves the retention of nitrogen in the animal, increasing in particular the liver stores of the animal.^{10,11} This optimum quantity of methionine varies with the magnitude of the sulfur stores and a large excess of the amino acid over that needed to fill these stores will even reduce the retention of nitrogen. Thus, addition of methionine to the diet may increase or decrease the retention of nitrogen, depending upon the state of the sulfur stores of the animal and on the quantity of amino acid added. Cox et al.,¹² Johnson and co-workers¹³ and Schwimmer et al.¹⁴ found that the addition of methionine to the diet of man did not increase the retention of nitrogen which can be interpreted to mean that the addition of methionine provided an excess above the demands of normal metabolic processes.

When a mixture of amino acids is presented to the internal environment of the animal, the amino acids become a part of the dynamic equilibrium which characterizes the living system. Thus, the need for external supplementation will depend upon the components of that equilibrium. Mitchell¹⁵ found, for example, that adding lysine to wheat gluten did not improve the retention of nitrogen in the adult rat. He suggested that the adult rat could synthesize lysine rapidly enough to take care of the needs for maintenance but that the young and growing rat could not. Lysine was indispensable to the young but not to the adult. Frazier et al.¹⁶ demonstrated, however, that lysine was essential for growth of new tissue in the protein-depleted adult rat. Lysine is definitely needed for maintenance in the adult man² and in the adult dog.⁶

Internal supplementation may explain some of the marked effects of unbalanced mixtures of amino acids on the body. A large excess of methionine added to casein in the diet will cause loss of nitrogen from skeletal tissues of the rat but will result in

TABLE II*

Nitrogen Source	Day	Dog 83		Dog 84	
		UN, mg./ day/ Kg.	K	UN, mg./ day/ Kg.	K
Protein-free.....	0-3	85	66	
Casein hydrolysate...	4	131	0.62	135	0.43
Casein hydrolysate...	5	141	0.54	112	0.62
Casein hydrolysate...	6	130	0.65	112	0.57
Casein hydrolysate...	7	118	0.75	100	0.68
Protein-free.....	8-10	88	61	

* Nitrogen source, days on experiment, nitrogen intake (AN), urinary nitrogen (UN) and nitrogen balance index (K). K is calculated from the equation $UN = (1 - K) (AN) + UNo$. The nitrogen intake was obtained by intravenous feeding of 120 mg. hydrolysate nitrogen per day per Kg. of body weight at the rate of 2 mg. N per minute per Kg. UNo is the excretion of nitrogen on a protein-free diet.

the building up of liver and kidney tissue. Similarly, Whipple and associates³³ suggest that an incomplete protein can be supplemented from reserve stores to produce cell or plasma protein. It is possible, therefore, that some tissues are torn down, supplying amino acids, to build up others.

Nitrogen Balance Indexes in Intravenous Feeding. Nitrogen balance indexes can be determined for protein hydrolysates fed intravenously as well as orally.¹⁷ These indexes are calculated from the following equation which is derived from (1) $UN = (1 - K) AN + UNo$; (2) when UN is urinary nitrogen, K is the nitrogen balance index, (AN) is absorbed nitrogen and UNo is the excretion of urinary nitrogen on a protein-free diet. The data recorded in Table II illustrate the calculation of the index of an enzymatic casein hydrolysate from equation 2. The dogs were fed a protein-free diet (70 calories/Kg. of body

weight) until the urinary nitrogen excretion was relatively constant, collections being made over a three-day period to determine an average UNO. The hydrolysate was fed intravenously for the next four days, 120 mg. of N/day/Kg. of body weight being infused at the rate of 2 mg. N/min/Kg. One hour after the infusion the dogs received the protein-free diet to keep their caloric intake constant. After four days of infusion the dogs were fed the protein-free diet again for three days to determine another average value for UNO. The values for K were calculated using the first UNO with UN for the fourth and fifth days and the last UNO for the sixth and seventh days.

The daily variation in values for K can be very great in dogs depending upon a number of factors, many of them being unknown. In one dog, for example, a casein hydrolysate had an average index of 0.5 which decreased suddenly to 0 and then to negative values, body nitrogen being lost. The excess loss of nitrogen was associated with an infection, the disappearance of which resulted in a return to a normal index. Toxic substances or anything that alters metabolic processes can alter the retention of nitrogen by the animal. There is a great need to determine the factors, especially in the sick animal, which can effect this retention.

The indexes for the hydrolysate fed intravenously into the protein-depleted dog are greater than in the normal animal, showing greater nitrogen retention in the depleted animal. (Table III.) Similarly, Silber et al.¹⁸ found that protein depletion increased the retention of amino acid nitrogen in the animal. The data in this table also illustrate the higher indexes obtained when the hydrolysates are fed orally than when they are infused intravenously. A different pattern of amino acids could be presented from the gastrointestinal tract than from the vein because of digestive and absorptive processes in the gut and of more direct action of the liver on the products absorbed from the intestine. Loss of amino acids or polypeptides

by excretion in the urine will reduce the index of the hydrolysate fed intravenously.

The rate of excretion of α amino nitrogen, ammonia and urea nitrogen and other forms of nitrogen during the day of infusion are illustrated in Fig. 3. The first hour in

TABLE III*
NITROGEN BALANCE INDEXES OF PROTEIN HYDROLYSATES
FED ORALLY OR INTRAVENOUSLY TO NORMAL DOGS OR
INTRAVENOUSLY TO DEPLETED DOGS

Hydrolysate	Nitrogen Balance Index		
	Normal		Depleted Intra- venous
	Oral	Intra- venous	
Commercial hydrolysate....	0.82	0.67	0.82
Casein hydrolysate.....	0.82	0.60	
Fibrin hydrolysate.....	0.81	0.66	
Fibrin (crude) hydrolysate..	0.60	0.36	0.53

* Some of these data were taken from a paper by Allison, Seeley and Ferguson.¹⁷

this figure represents the rate of excretion of the various forms of nitrogen before the infusion was started. The infusions were given during the first to third hours. The black blocks represent the rate of excretion of α amino nitrogen; the blocks with slanted lines, the rate of excretion of ammonia plus urea nitrogen and the white blocks, the excretion of other forms of nitrogen. These data were obtained during infusion of a fibrin hydrolysate in which 57 per cent of the nitrogen was in the form of polypeptides.

The figure illustrates the marked rise above control values in the rate of excretion of α amino nitrogen and of ammonia and urea nitrogen during and after the infusion. The rate of excretion of α amino nitrogen fell rapidly toward control values within an hour after the infusion ended. The rate of excretion of urea and ammonia nitrogen continued to rise after the infusion, returning to control values several hours thereafter. The excretion of other forms of nitrogen increased also during and for

several hours after the infusion. This increase was due to polypeptide nitrogen not utilized by the animal. Loss of amino acids and peptides (if the latter are present) through excretion in the urine are greater, the higher the rate of infusion. If the essen-

increased by the reduction in caloric intake, leaving a smaller proportion of the absorbed nitrogen for the development of new tissue.

The nitrogen balance indexes of the dietary protein or hydrolysate are not altered in the dog until the caloric intake has been reduced to less than 50 per cent of normal.⁴ This normal caloric intake varies with the breed and activity of the dog averaging 70 calories/Kg. of body weight. Some breeds, particularly the smaller active ones such as the fox terriers, require 100 or more calories/Kg. of body weight, but the critical caloric intake below which nitrogen retention falls rapidly is usually around 35 calories/Kg. A similar reduction in retention of dietary nitrogen with decreased caloric intake has been found in the rat by Willman et al.²⁰ and in man by Schwimmer and associates.² The latter workers demonstrated that young men fed a semisynthetic diet containing egg white retained the dietary nitrogen if the intake was 1,500 to 1,800 or more calories but did not do so on intakes of 900 calories. Retention of nitrogen was obtained, however, at the lower caloric intake if the nitrogen and fat contents of the diet were sufficiently high. Willman et al.²⁰ also reported that the retention of nitrogen in the rat was improved on a restricted diet if the fat content was high.

Benditt et al.²² studied "the interrelationship between protein and caloric intakes and their influence upon the utilization of ingested protein for tissue synthesis by the adult protein-depleted rat." They also found a critical level of caloric intake below which the retention of nitrogen was restricted. This critical level was approximately 1,240 calories/sq. M./day. They concluded from their studies that "the fabrication of a kilogram of tissue on a growing rat and the reconstruction of a kilogram of tissue in the adult protein-depleted rat demand the same quantities of structural material and similar constructing energies." They concluded further "that the rate of protein utilization is independent

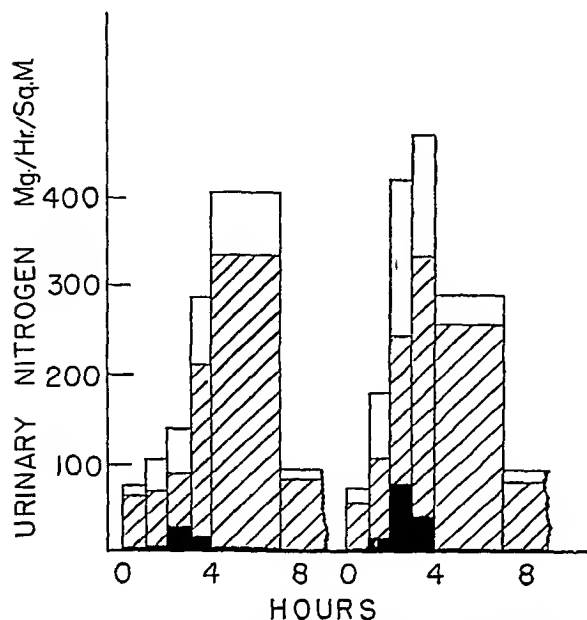


FIG. 3. The rate of urinary nitrogen excretion (mg./hr./sq. M.) are plotted against time in hours; 120 mg. of hydrolysate nitrogen per Kg. of body weight were infused the first to third hours. The black blocks represent the rate of excretion of π amino nitrogen, the blocks with slanted lines the rate of excretion of urea plus ammonia nitrogen and the white blocks the rate of excretion of other forms of nitrogen.

tial amino acids are well above threshold concentrations, however, the rate of infusion has no effect on the nitrogen balance index.

Effects of Caloric Intake. Retention of nitrogen in the animal also is a function of caloric intake. The urinary nitrogen excretion increases, for example, in the dog³ and in man¹³ if the caloric intake is lowered below optimum. A reduction in caloric intake, therefore, increases the excretion of nitrogen from body stores. Bosshardt et al.¹⁹ demonstrated that the growth of nitrogen in the tissues of the rat and the mouse was maintained over a range of caloric intake but that decreases below that range resulted in a reduction in the formation of new tissue. They pointed out that the excretion of body nitrogen may be

of the caloric intake at caloric intake levels above those which supply the needs for maintenance, synthesis, storage, and waste."²³

Elman,²⁴ however, has pointed out that "fatty tissue may readily furnish a good deal of the daily caloric intake." He demonstrated in dogs "that the amount of energy supplied may be drastically reduced without leading to depletion of essential protein tissue, provided a sufficient amount of protein is given. Under these conditions the energy requirements are obviously made to come from tissue fat, whose depletion leads to no physiologic impairment."

Effect of Degree of Hydrolysis. The question is often asked as to whether or not a protein hydrolysate fed orally is utilized as well or better than the natural protein. The indexes of unsupplemented acid hydrolysates are always lower than the protein of which they are made because acid hydrolysis destroys essential amino acids such as tryptophane. Most acid hydrolysates can be reconstituted by addition of optimum amounts of tryptophane and sometimes methionine. There are data in the literature which support the belief that hydrolysis destroys some essential polypeptide or other constituent of the protein not identified as an amino acid. Miller, Robschert-Robbins and Whipple²⁵ present data which can be interpreted to mean that there is some unidentified substance present in dietary proteins, absent in mixtures of amino acids, which effects the retention of nitrogen in the animal. Similarly, Womack and Rose²⁶ have evidence that protein may contain substances, not found in amino acid mixtures, which promote maximum growth of rats. Recently, Wooley^{27,28} found one or more polypeptides called streptogenin in intact proteins essential for optimum utilization of nitrogen by the mouse. Frazier et al.,¹⁶ on the other hand, found a mixture of amino acids just as adequate as natural protein for regeneration of tissue proteins in the protein-depleted rat. Chow, Allison and White²⁹ have demonstrated that the utilization of casein by the dog and rat is not altered by enzymatic hydrolysis,

the hydrolysates having the same nitrogen balance indexes and growth-promoting values in dogs and rats as the unhydrolyzed casein. Enzymatic hydrolysis, which released at the most only 60 per cent of the available amino acids, did not alter the streptogenin content of the casein and would not necessarily alter other essential polypeptides. Complete hydrolysis might, therefore, have lowered the nutritive value by destroying these peptides. Experiments involving synthetic patterns of amino acids or reconstituted acid hydrolysate indicate, however, that peptides like streptogenin are not indispensable but may, at times, improve utilization of an amino acid mixture by increasing the nitrogen intake or by supplying an additional quantity of essential substances that cannot always be synthesized in adequate quantities by the animal.

Significance of a Positive Nitrogen Balance. Growth of new tissue, whether in the young or adult animal, cannot take place, no matter what the pattern of amino acids may be, unless sufficient nitrogen is given to place the animal in positive nitrogen balance. An examination of Figure 2 demonstrates that the largest positive nitrogen balances are produced in the protein-depleted dogs. The growth in nitrogen, in other words, continues in a linear fashion well on the positive side of nitrogen balance. Much more nitrogen is needed by a depleted than a normal animal, and much more can be fed to such a system before it is all wasted in catabolism. The more the protein stores are filled the less growth can be experienced in the region of positive nitrogen balance in the adult animal. Theoretically, if the stores are all saturated, the adult animal cannot be put into positive nitrogen balance. The aim in protein nutrition is to fill the stores so that they can be maintained by a relatively small daily intake of a good pattern of amino acids. Few animals are in that ideal nutritional state, most of them being deficient in tissue proteins some place in the body.

The data plotted in Figure 4 illustrate the facts (1) that there is an upper limit to the growth in nitrogen that can be obtained by feeding a protein source and (2) that a much greater maximum balance can be obtained with a good pattern than

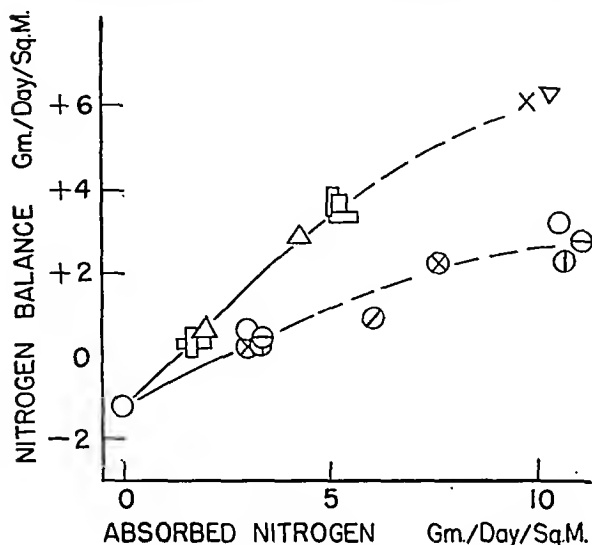


FIG. 4. The circles describe data obtained while feeding wheat gluten to protein-depleted dogs, the angular symbols describe similar data obtained while feeding whole egg. The data are expressed as Gm./day/sq. M. of body surface area.

with a poor pattern of amino acids. The angular symbols in this figure illustrate data obtained while feeding a dried defatted whole egg preparation to protein-depleted dogs. The maximum positive nitrogen balance that could be obtained by feeding this nitrogen source was approximately 6 Gm./day/sq. M. of body surface area. Feeding larger amounts than those required to produce the maximum, is not an efficient way to replete the animal. The circles represent data obtained while feeding wheat gluten to another group of depleted dogs. The maximum positive nitrogen balance that could be produced by this nitrogen source was less than 3 Gm./day/sq. M. Again there was no need to feed more than the amount necessary to produce this maximum. The filling of the protein stores with wheat gluten is, therefore, a much slower process than with the whole egg preparation. Each pattern of amino acids has an upper limit for utilization by the animal.

Effects of Depletion in Proteins. Depletion in proteins results in the general reduction in the so-called protein reserves of the body, in labile liver cytoplasm, in plasma albumin, in hemoglobin, in plasma gamma globulin and in the nitrogen of the other tissues of the body. The loss in liver nitrogen is rapid and marked when an animal is placed on a protein-free diet.³⁰⁻³² The total circulating plasma albumin decreases under a condition of nitrogen deficiency reflecting the loss of nitrogen throughout the body of the animal. There is, in other words, an interchange between the nitrogen of the body which is expressed as a dynamic equilibrium, a steady state which has been emphasized by the work of Whipple and associates.³³

Total plasma proteins will vary approximately from 5.8 to 7.5 Gm. per cent averaging 6.5 Gm. per cent in an heterogeneous group of so-called normal dogs. Although plasma protein concentrations are not absolute measures of the magnitude of protein stores, values less than 5.8 Gm. per cent usually represent a state of depletion in proteins. The decrease of plasma protein below that value is a result of a decrease in plasma albumin and in the beta and gamma globulin fractions. The alpha globulin fractions, on the other hand, increase in concentration as the protein stores are depleted. One dog, for example, had the following percentages of plasma proteins under control conditions on an adequate diet: total plasma proteins, 6.0; albumin, 2.5; alpha globulins, 0.9; beta globulins, 2.0; gamma globulin, 0.6. After several weeks on a protein-free diet these values had changed to: total protein, 3.8; albumin, 1.0; alpha globulins, 1.6; beta globulins, 0.9; gamma globulin, 0.3. The electrophoretic patterns of plasma proteins from a dog before and after depletion and after repletion in proteins by feeding casein are illustrated in Figure 5.³⁴ The tall peak representing the albumin fraction is markedly reduced in the depleted dog and is returned to normal by repletion.

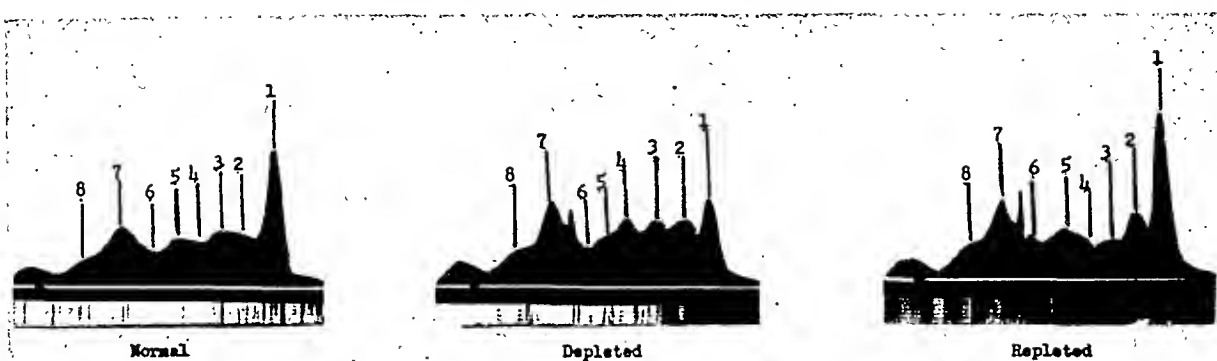


FIG. 5. Electrophoretic patterns (descending) of plasma from a dog before and after depletion in proteins and after repletion of casein. The numbers indicate the components: albumin 1; α_1 globulin 2; α_2 globulin 3; β_1 globulin 4; β_2 globulin 5; β_3 globulin 6; fibrinogen 7; γ globulin 8. These studies were done in cooperation with Dr. B. F. Chow of The Squibb Institute for Medical Research and the electrophoretic patterns were obtained by him.

Thus, the degree of depletion is correlated well with the fall in the albumin/globulin ratio because the albumin fraction is markedly reduced while the globulin fraction is not. The increase of the α -globulin fraction of the plasma is the result of the fall in plasma volume not of a rise in total circulating α globulin. The total amount of this globulin fraction rarely changes significantly in the dog until the animal has been so severely depleted in proteins that liver damage is quite marked; repletion is difficult, the animal often dying in the depleted state. The decrease in plasma albumin and increase in α globulin have also been found to be associated with malnutrition, tuberculosis or cancer in man.³⁵ The γ globulin fraction is reduced below normal in the depleted dog, a reduction which is accompanied by an increased susceptibility to infection. These infections can be treated and the growth of invading pathogens halted but the animal cannot develop a resistance to the invasion without repletion in proteins.

Associated with the decrease in plasma albumin in the depleted animal is a reduction in plasma volume and an increase in the extracellular fluid.³⁶ For example, one dog under control conditions had a plasma volume of 625 ml. and an extracellular fluid volume of 3,500 ml. Following depletion in proteins, the plasma volume had dropped to 502 ml. while the extracellular fluid volume had increased to 4,400 ml. Even with this marked increase in extra-

cellular fluid, edema could not be detected clinically. Nutritionally edema is not clinically evident in dogs until it is severe.

Because of the fall in plasma volume, however, the plasma protein may be concentrated to such an extent that hypo-

TABLE IV*

	Plasma Protein, Gm. %	Plasma Volume, ml.	Total Circulating Albumin A, Gm.	Total Circulating Globulin G, Gm.	A/G
Control...	7.04	430	16.6	13.6	1.2
Depleted..	5.94	349	6.4	13.1	0.49
Repleted..	6.16	470	15.6	13.2	1.2

* Data to demonstrate that marked hypoproteinemia in the dog does not always accompany protein depletion. The effects of depletion and repletion on total circulating albumins, globulins and the A/G ratio are also recorded.

proteinemia does not develop. The plasma protein concentration of a normal dog, for example, was 7.04 Gm. per cent. (Table iv.) The plasma volume was 430 ml., the total circulating proteins equaling 30.2 Gm. After depletion in proteins the plasma protein concentration was 5.94 Gm. per cent, still within the normal range. The relatively high plasma protein concentration was the result of the marked fall in plasma volume to 349 ml. The total circulating proteins had decreased to 19.5

Gm., 6.4 of which was albumin and 13.1 globulin.

In their studies on the effect of protein depletion in dogs Whipple, Robscheit-Robbins and Miller^{33,37} have used a so-called doubly depleted animal. This double depletion is produced by sustained bleeding of dogs fed a protein-free or low protein diet with adequate iron. The reserve stores of blood protein producing materials are depleted by maintaining levels of 6 to 8 Gm. per cent of hemoglobin and 4 to 5 per cent of proteins. They state that "the body guards jealously the fabrication of hemoglobin and, given a real need for both plasma protein and hemoglobin (anemia and hypoproteinemia of double depletion), the protein flow favors hemoglobin." They have also shown that doubly depleted dogs will continue to produce much plasma protein and hemoglobin for many weeks while being fed a protein-free diet. Thus, the blood proteins take priority over other tissue proteins, an example of the "ebb and flow" between tissue and blood proteins. The transformation of tissue proteins into blood proteins caused a loss in body weight, the average dog tolerates raiding of body tissue proteins from seven to eleven weeks.

The quantity of protein in the liver is lost most rapidly when animals are placed on a low nitrogen or protein-free diet. Liver function decreases in the depleted animal. Kosterlitz³² demonstrated that this loss was associated with a reduction in liver cytoplasm and Li and Freeman^{38,39} have shown that fatty livers developed in dogs fed a 33 per cent fat protein-deficient diet for ten to sixteen weeks. They also found the incidence of peptic ulcers high in protein-deficient dogs.⁴⁰ Armstrong and Estremera⁴¹ found that bone atrophy develops in adult rats fed a protein-deficient diet. Corneal vascularization develops also in protein deficiencies, proving that corneal tissue like all other tissues of the body requires the proper daily pattern of amino acids in the diet to maintain its integrity.^{42,43}

Weech⁴⁴ and Saehar et al.⁴⁵ have shown that there is a constant relationship between

the loss from plasma proteins and from the rest of the body during protein depletion, for every Gm. of plasma protein lost approximately 30 Gm. are lost from other body tissues.

Repletion in Proteins. When the animal is repleted, nitrogen is replaced in the body

TABLE V*

Dog No.	Nitrogen Ingested, Gm./sq.M.	Nitrogen Excreted, Gm./sq.M.	Body Nitrogen Gained (B.N.G.) Gm./sq.M.	Plasma Protein Nitrogen Gained (P.N.G.) Gm./sq.M.	P.N.G. B.N.G. $\times 100$ Per Cent
28	189.0	88.6	100.4	3.06	3.05
42	174.0	81.0	93.0	2.83	3.04
44	192.0	95.8	96.2	2.84	2.95
63	176.2	83.6	92.6	4.29	4.63
74	175.1	88.2	86.9	2.11	2.43

* Dogs depleted in proteins were repleted for thirty days with whole egg protein. Nitrogen ingested, nitrogen excreted and body nitrogen gained during this repletion period are recorded. Plasma protein nitrogen gained and the per cent of the body nitrogen gained which is represented as plasma protein nitrogen are listed.

tissue proteins and the plasma proteins in the same ratio of 30:1. This ratio is illustrated in Table v. These data were obtained on depleted dogs which were repleted for thirty days with whole egg protein. The difference between ingested and nitrogen excreted is recorded as nitrogen gained. The body nitrogen gained by these dogs over the thirty-day repletion period varied from eighty-seven to one hundred, averaging 93.8 Gm./sq. M. body surface area. The average plasma protein concentration at the end of the repletion period was 6.2 Gm. per cent which is an average for most normal dogs. The total increase in plasma protein nitrogen during the repletion period varied from 2.1 to 4.3, averaging 3 Gm. per sq. M. This increase in plasma protein nitrogen represented an average of 3.2 per cent of the body nitrogen gained. Thus, approximately one-thirtieth of the

nitrogen gained was represented as plasma proteins, principally albumin.

The type of protein found in the tissue and in the plasma can vary, however, according to the pattern of amino acids fed to the animals. Seeley⁴⁶ found, for example, that the oral feeding of beef serum protein favored repletion of plasma albumin while casein promoted the formation of both albumin and globulin. Similar results were reported by Holman et al.⁴⁷ and by Madden and Whipple.⁴⁸ Chow et al.⁴⁹ demonstrated that oral administration of a casein hydrolysate brought about an increase in both albumin and globulins, increasing the globulins even above normal values in dogs. Lactalbumin hydrolysate, on the other hand, favored regeneration of the albumin fraction. It has been pointed out previously that imbalances between the essential amino acids can bring about internal supplementation, leading to the reduction of one kind of tissue nitrogen and to the building up of others. Cannon and associates have demonstrated that the same amino acids which are essential for growth in the rat are also indispensable for repletion of body tissue in the protein-depleted rat although the proportions vary according to the state of depletion and physiologic state of the animal. Cannon⁵⁰ emphasized that all of the amino acids necessary to synthesize tissue protein must be present simultaneously, in adequate amounts and in the proper proportions. The dietary essential amino acids become a part of the dynamic equilibrium which characterizes protein metabolism, repletion of tissue proteins being a function of the pattern of amino acids introduced into this equilibrium.

COMMENTS

The protein stores are the proteins of the tissue cells and the fluids which bathe them, forming a dynamic equilibrium so that the body, as a whole, is a reservoir for the nitrogen needed to maintain the integrity of its protoplasm. These stores are reduced in malnutrition or disease and in their reduction the body loses capacity to repair

damage, to build antibodies and to maintain the mechanisms which create barriers to destructive forces. It is a function of the diet, of protein therapy, to replenish these stores. There are no reserves of essential amino acids which can be drawn upon to supplement an inadequate diet without breaking down body proteins so that dietary sources lacking one or more of these acids cannot fill the reservoir. It is filled by simultaneously presenting to the body all of the essential amino acids in the proper proportions and amounts. Growth and regeneration of destroyed tissues take place only in the presence of sufficient nitrogen to create a positive nitrogen balance. Dietary sources for nitrogen whether they are proteins, hydrolysates or mixtures of amino acids are evaluated, therefore, according to their ability to promote the maintenance, repair and growth of body tissues.

The protein stores are reduced in the depleted state and they are different in character than in the normal individual. Less dietary nitrogen is needed to maintain the depleted than the normal state, and the potentialities for growth increase upon depletion. Indeed, the degree of depletion can be estimated by the magnitude of positive nitrogen balance that can be produced. It is the function of protein therapy to provide an optimum pattern of amino acids to fill these stores as uniformly as possible. There is a maximum rate at which each protein or pattern of amino acids is capable of promoting the growth in nitrogen; feeding more than the amount necessary to produce the maximum rate is inefficient and may at times place a catabolic and excretory burden upon the individual.

The reservoir of body nitrogen, being composed of the tissues, is a series of compartments with differing capabilities for supplying nitrogen to the metabolic pool. Some tissue proteins, such as the albumins, are more labile in providing nitrogen to this pool than are others such as certain globulins. Different amino acid patterns

can favor the filling of one compartment over another, even depleting one while filling a second. Thus, different amino acid patterns can do different jobs in the body.

Finally, it cannot be overemphasized that protein therapy is an integral part of an overall diet therapy. Energy, derived from carbohydrates and fats, is needed to drive the mechanisms which rebuild or develop new living tissues. Fats and carbohydrates spare dietary and tissue nitrogen. Enzymes are built from amino acids, with vitamins as well as certain amino acids providing the active spots for catalysis. A vitamin deficiency can lead to marked reduction in protein stores. All constituents of the diet, therefore, including the minerals and water, play important roles in the maintenance, repair, and growth of living tissues and in the promotion of the well being of the animal. A new era of integration is developing in nutrition.

SUMMARY

1. The protein stores of the animal are the labile cytoplasmic proteins in the tissues and body fluids, cellular nitrogen being drawn upon to maintain the nitrogen integrity of essential tissues.

2. The amount of nitrogen excreted from the protein stores during the feeding of a protein-free ration decreases as the stores are depleted. Less dietary nitrogen is needed to maintain nitrogen equilibrium in a depleted than in a normal animal.

3. The relationship between absorbed nitrogen and nitrogen balance is linear in the region of negative nitrogen balance becoming curvilinear in the region of positive balance. The slope of this line, called the nitrogen balance index, is a function of the retention of nitrogen in the body of the animal, the index increasing as the retention increases. The index evaluates the retention of dietary nitrogen for the overall filling of the protein stores of the animal.

4. As the protein stores decrease the linear relationship between nitrogen balance and absorbed nitrogen extends further and further into the region of positive

nitrogen balance, the greater the positive balance the greater the degree of depletion in proteins. Different patterns of amino acids fill the stores at different rates. Feeding a protein source above an amount which produces maximum filling, is inefficient.

5. Supplementation of proteins and protein hydrolysates with amino acids can improve the indexes but imbalances produced by the addition of abnormal amounts of amino acids may cause loss in body nitrogen. It is possible under conditions of imbalance to build up one tissue while another is being torn down.

6. Hydrolysates or amino acid mixtures fed intravenously have a lower index than when fed orally. The higher oral index is due, in part, to the effects of digestive and absorptive processes in the gut and more direct action of the liver on the products absorbed from the intestine. The increased urinary excretion of amino acids and peptides following intravenous feeding does not usually affect the index significantly.

7. The retention of dietary nitrogen is a function, too, of caloric intake. There is a critical level of caloric intake (approximately 50 per cent of adequate) below which the retention of nitrogen is markedly reduced.

8. The retention of nitrogen fed orally is not affected by the degree of enzymatic hydrolysis of the protein.

9. Depletion in proteins results in reduction in protein stores of the body, labile liver cytoplasm, plasma albumin, hemoglobin, plasma gamma globulin and in the nitrogen of the other tissues of the body. Thirty times as much nitrogen is lost from the body tissues as from the plasma. A shift in body fluids accompanies the depletion, resulting in a nutritional edema accompanied usually by a fall in plasma volume. The decrease in plasma volume can be so great that hypoproteinemia does not develop.

10. When the animal is repleted, the nitrogen is retained in the body tissue proteins and plasma proteins in the ratio of 30:1. Restoration of tissue nitrogen is a

function of the patterns of amino acids which are given, different patterns producing different rates of repletion of the various protein stores.

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Combined Staff Clinics

Peripheral Vascular Disease

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. FREDERICK K. HEATH: The subject of this clinic is a consideration of the genesis and therapeutics of arterial vasospasm in peripheral vascular disease but before beginning the discussion a few introductory remarks may be in order.

Despite the fact that the extremities make up about 35 per cent of the total body mass and 65 per cent of the body surface, peripheral vascular disease has never been a popular medical specialty. This stepchild of medicine remains largely a subject for clinical observation, statistical analysis and shotgun therapy. Emphasis has been placed on empiricism, dogmatism and treatment so that the literature is voluminous, conflicting and unreliable. Clinical investigators who have turned their attention to the solution of vascular mechanisms have been few in number; the investigative literature dealing with functioning of the blood vessels and blood flow in quantitative terms is small indeed and prior to 1930 almost non-existent. Not only do the diseases of the vessels seem to present insoluble problems of etiology and rational therapy but because of the lack of adequate investigative methods they often defy serious analysis.

What are those conditions so loosely assigned to the limbo of peripheral vascular disease? In a general way one may delineate two main groups: (1) those resulting from organic disease of the blood vessels causing narrowing of the lumen with reduction in blood flow of a permanent character and (2) those showing no organic change in the blood vessels but characterized by an obvious decrease in blood flow which is reversible and due to temporary narrowing of the lumen by spasm. The

first group includes arteriosclerosis and thromboangiitis obliterans, each of which may have a superimposed spastic component. The second group is comprised of Raynaud's syndrome, scleroderma, livedo reticularis, acrocyanosis, and spastic phenomena associated with cervical ribs, scalene syndrome, embolism, thrombosis and thrombophlebitis, Sudeck's atrophy, shoulder-hand syndrome and trauma.

Since all these states are associated with a reduction in the rate of arterial blood flow, it becomes important to examine the methods available to measure this factor. Qualitative information is easily obtained. The color of the skin depends on the state of the capillaries and first venous subpapillary plexus, the rate at which these vessels are filled or emptied and upon the oxygen saturation of the blood. The temperature of the skin is an index of the rate of blood flow through it. Thus marked narrowing but not obliteration of a main arterial trunk to an extremity produces pale, cold skin. On dependency, redness and then cyanosis may be added if not already present. With sympathetic activity, in certain spastic states, there may be sweating as well. Attendant upon the collateral supply, the level at which the arterial inflow is reduced may be determined by simple inspection or by noting the skin temperature or the fullness of the pulse of the artery supplying the extremity.

With involvement of arteries of smaller caliber, essentially the same picture results. Thus in Raynaud's syndrome spasm of the digital arteries first produces pallor and coldness of the skin of the fingers, the blood pools in the capillaries and becomes anoxic,

with resulting dilatation of the capillaries and venules and the appearance of a blue color. Immediately following the spasm, when the arterial inflow returns to normal, the skin is hot and red since the wide open minute vessels do not immediately regain their tone and so become filled with relatively fast-moving oxygenated blood.

The cold, wet, blue hands and feet of acrocyanosis are thought to result from spasm of the arterioles and small venules with capillary dilatation and stagnation of the blood. The mottled blue skin of livedo reticularis is similarly believed to be the result of spasm of the smaller vessels.

Much information, therefore, can be gained by visual and tactile means. Some of the more objective procedures furnish relatively little more information. Thus measurements of skin temperature simply put into objective terms what may be somewhat less accurately gauged with the hands and like the more simple procedures it furnishes information only in regard to the blood flow to the skin. To interpret differences in skin temperature before and after a procedure designed to produce vasodilatation it is essential that the determinations be made under identical conditions of environmental temperature in which the patient is allowed at least thirty minutes to approach a state of equilibrium. Even here the skin temperature of the digits may vary widely, dependent upon shunting in response to a multitude of factors such as emotion, smoking and ingestion of food. Under standard conditions, i.e., room temperature 25°C., average values for the fingers are in the vicinity of 32° to 35°C., with the toes somewhat lower but usually above room temperature. Nearer the trunk, skin temperatures are higher.

Oscillometry is designed to measure the volume of the pulses. The instrument consists of a sensitive needle which fluctuates over a unit scale in response to the arterial pulsations in an extremity transmitted through a pressure cuff, the principle resembling that of the ordinary blood pressure manometer. However, in the case

of the oscillometer readings are taken over a variety of pressures and only the maximal deflection is significant. Normal values differ from patient to patient, from instrument to instrument and from observer to observer. The range in the thigh may approximate 4 to 15 units, the leg 3 to 12, the ankle 1 to 10 and the foot from 0 to 3; readings in the arms are comparable to the legs. The oscillometer is often expected to yield more information than it can. It simply measures the amplitude of the pulsation in relatively large vessels and hence may be useful to verify the presence or absence of a doubtful pulse or to mark the level of arterial obstruction. To interpret the size of the excursion in terms of blood flow is erroneous since the oscillometric readings may be small or absent with obstruction of a main artery yet adequate small vessel collateral flow may exist; conversely, with marked vasodilation increase in oscillometric readings may occur with actual reduction in total flow due to a disproportionate increase in the backflow phase.

Arteriography with diodrast or other contrast medium is an elaborate, expensive method of outlining the blood vessels. In certain instances, for example the demonstration of aneurysm or arteriovenous communications, it may be most helpful. On the other hand, it suffers from two main objections: the distinction between spasm and thrombosis is difficult and it yields no information as to the rate of blood flow.

One interesting method of obtaining qualitative although not quantitative data on blood flow is the use of radioactive sodium intravenously with subsequent periodic determinations of the Geiger count over certain areas of the extremities. In this fashion a curve may be obtained (Fig. 1) which may be useful as a baseline to estimate objectively the effect of therapeutic or investigative procedures on blood flow in any given area.

Quantitative measurement of the blood flow to the extremities is difficult. The use of A-V O₂ difference is not applicable to

the limbs because of the extensive and variable shunting which takes place in the hand and foot and which is not subject to control or measurement. At the present time the venous occlusion plethysmograph, which is slow and cumbersome and can be

crease in distal limb volume which occurs when the venous return is obstructed proximally by a pressure sufficient to occlude the venous outflow but not the arterial inflow. The results are recorded with reference to standard room and bath

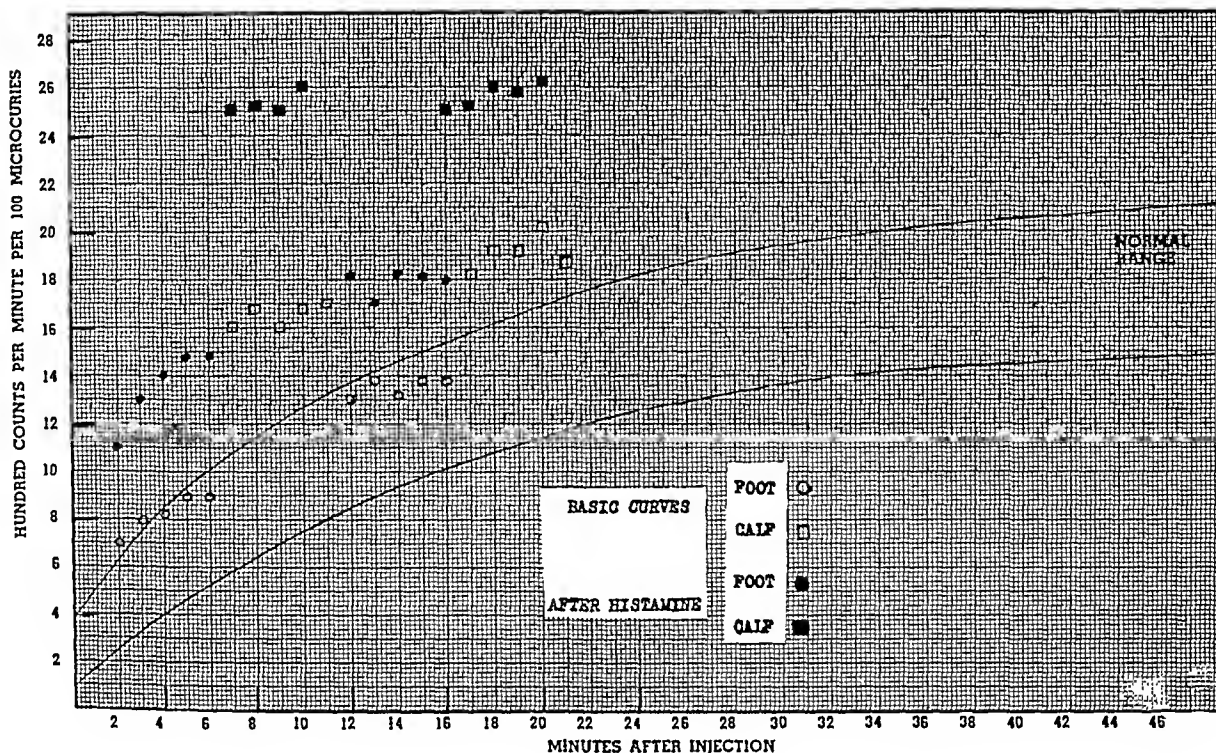


FIG. 1. Radioactive sodium circulation test shows how an intra-arterial infusion of histamine can cause an increase in the Geiger count over the foot and calf of a patient with arteriosclerotic endarteritis obliterans of the popliteal artery.

used only in the resting state, furnishes the most reliable quantitative results. This instrument consists of an insulated water-tight shell shaped to contain a part of an extremity and designed to record the in-

TABLE I
BLOOD FLOW IN CC./MIN./100 CC. LIMB VOLUME; ROOM TEMPERATURE 25°C.

	Bath Temperature	
	32°C.	43-45°C.
Finger.....	15-40	90.
Hand.....	9.3-2.1	22.
Forearm.....	1.8-0.7	7.9
Foot.....	1.2 to 2.8	18.1
Leg.....	1.4-0.5	3.6

temperatures in terms of cc. of blood flow per minute per 100 cc. of limb volume. Obviously, the plethysmograph may be adapted to segments of a limb in order to obtain the flow in certain areas. With it much valuable information has been obtained. Table I¹ indicates the approximate blood flow in the extremities in the normal resting state and emphasizes the volatile nature of the shunts.

No simple method yet available enables one to differentiate between blood flow to skin and that to muscle, a point which is significant in the problems of intermittent claudication. In such an instance use of a standard walking tolerance test gives the

¹ ABRAMSON, DAVID I. Vascular Responses in the Extremities of Man in Health and Disease. P. 80. Chicago, 1944. University of Chicago Press.

best information although if the total blood flow to a segment of an extremity is known it may be possible from anatomic considerations to approximate the proportional flow. Thus it has been shown by Abramson² that in the finger almost all the blood flow is through skin, in the hand the skin predominates 2:1 and in the forearm muscle predominates about 4:1. The foot resembles the hand while in the leg, muscle is even more predominate than in the forearm.

Recently Barcroft and Edholm³ have produced vasoconstriction of the skin by adrenalin iontophoresis and then measured the increased blood flow of the sympathetic supply after block by procaine. Using this method and the anatomic data of Abramson, they estimate that blood flow to forearm muscle is doubled following removal of vasoconstrictor tone.

STUDENT: How does one differentiate clinically between organic obstruction to blood flow and spasm?

DR. HEATH: The most reliable method is by measurement of blood flow or exercise tolerance before and after procaine block of the regional somatic or sympathetic pathways. Dr. Bridges will discuss some of these problems from the point of view of the neurosurgeon.

DR. THOMAS BRIDGES: Raynaud's disease is the most characteristic example of peripheral vascular disease due to vasospasm. The smaller arteries of the distal portion of the extremities are most often the site of this intense vasospasm. However, arteries of the head and viscera may be involved. The involvement is symmetrical, that is, symptoms occur simultaneously in both hands or both feet. There is no occlusion of arteries or arterioles, at least early in the disease. The vasospasm causes coldness, cyanosis and, ultimately, tissue breakdown, gangrene, scarring or scleroderma. Cold temperatures and emotional crises aggra-

vate the vasospasm. Women are affected primarily, the disease occurring rarely in men.

A typical case history is that of a thirty-eight year old divorcee who was admitted to the hospital complaining of aching and burning pain in both hands, of four years' duration, sometimes better and at other times much worse. Upon examination both hands were cold to the touch and there was a cyanotic hue to the fingers. All of the fingers had atrophic, shiny skin and both hands were constantly moist. Exposure to cold and emotional upsets resulted in blanching of the terminal phalanges. Over the tips of two fingers of each hand were small areas of dry, superficial ulceration which had appeared during the preceding three months. Stellate ganglion novocain block was effective in increasing the temperature of the corresponding hand and changing the slight cyanosis to a pink color. Bilateral thoracic preganglionic sympathectomy has been effective in maintaining good color and freedom from pain during the past winter.

Vasospasm of intensity almost equal to that seen in Raynaud's disease is encountered in an extremity in which there has been sudden occlusion of a major artery or vein. The occlusion may be due either to embolus or thrombosis or to trauma involving the vessel. The vascular tree may be quite normal prior to the sudden accident. The vasospasm is a primary neurovascular reflex, the stimulus arising from the area of vascular injury and sending impulses by way of viscerosensory nerves to the cord. The effector arc of this reflex is by way of the vasoconstrictor sympathetic nerves. Mass discharge is rarely seen and the vasospasm is generally limited to the extremity with the injured vessel. The usual signs of vasospasm occur: coldness, cyanosis, increased moisture of the skin. Oscillometric readings and arterial pulses are depressed by occlusion of a major artery but may not be depressed by the vasospasm of small vessels secondary to venous thrombosis or thrombophlebitis.

² ABRAMSON, D. I. and FERRIS, E. B., JR. Responses of blood vessels in the resting hand and forearm to various stimuli. *Am. Heart J.*, 19: 541, 1940.

³ BARCROFT, H., ET AL. On sympathetic vasoconstrictor tone in human skeletal muscle. *J. Physiol.*, 102: 21, 1943.

Acute thrombophlebitis is accompanied by varying degrees of vasospasm more pronounced distal to the area of phlebitis.

A typical case history is that of a fifty-three year old man who was admitted to the hospital with marked bilateral varicosities. On the third hospital day, while on conservative treatment, the right leg suddenly became pulseless, cold, cyanotic and slightly painful. No arterial pulses were felt. A diagnosis of arterial thrombosis close to the iliofemoral junction was made. Right lumbar novocain sympathetic block was performed at the level of the first and second lumbar ganglia. Within thirty minutes the right foot became dry, slightly pink and more comfortable. The superficial foot veins dilated and the skin temperature rose 3°C. Arterial pulses were still absent. The block improved circulation to this extremity by opening collateral arteriolar connections.

It is interesting to speculate on the significance of this vasospasm secondary to blood vessel disease which seems so deleterious to the individual. It should be remembered that this reflex mechanism would be effective in decreasing blood loss from laceration or crush injuries involving major vessels and as such is a primary defense mechanism. If wound repair is rapid, collateral and primary circulation is restored before this vasospasm can produce serious consequences. It is probably a more valuable reflex system in lower animals.

Closely related to the vasospastic phenomena seen with direct vascular injuries are those grouped together under the term reflex sympathetic dystrophies. The most common examples of this group are traumatic arthritis (or Sudeck's atrophy) and the shoulder-hand syndrome. In these, vasospasm is generally less intense but more chronic than that which occurs after sudden vascular insult. The stimulus for this vasoconstriction arises from injury to a joint. The injury is generally mild, being only a strain or an acute articular inflammatory reaction of short duration. In addition to the usual signs of vasospasm there is overactivity of sweat glands with marked

sweating over the distal part of the involved extremity. In cases of Sudeck's atrophy these changes are apparent in the foot and lower leg and most often follow a mild sprain or ankle "strain." The shoulder-hand syndrome is one in which evidence of sympathetic overactivity is seen in the hand and forearm following arthritis or bursitis of the shoulder, occasionally also after myocardial infarction.

A typical case of Sudeck's atrophy occurred in a nineteen year old seaman who was first seen six months after spraining his right ankle when he missed a step while descending a ship's ladder. X-rays had been negative for fracture or joint separation. He was able to walk for two days after the injury but was unable to bear weight on this ankle subsequently, despite intensive physiotherapy, strapping, casts with walking calipers and the like. At the time of our first examination the right foot was slightly swollen to above the ankle. The foot was very moist, cold and slightly cyanotic. There was no active motion at the ankle and passive motion was extremely painful. The patient refused to attempt to bear weight on this foot. X-rays revealed osteoporosis of the bones of the foot and lower leg. Novocain sympathetic block allowed slight passive ankle motion without pain. Two days after sympathectomy weight bearing was permitted and three weeks later complete motion of the ankle and full weight bearing had been restored. At that time the foot was dry, warm and pink.

A second group of vasospastic disorders which have been considered a type of reflex sympathetic dystrophy are those associated with spinal cord and peripheral nerve diseases. Poliomyelitis, peripheral nerve injuries, cervical rib compression of the brachial plexus and spinal root compression by herniated nucleus pulposus are among the common antecedent conditions for this type of vasospastic disorder. Pain is the presenting symptom and is of the "cramp-like" type, generally called intermittent claudication. This pain occurs either after exercise or when the patient is asleep. It is

considered to be due to a relative increase in demand for blood supply in the face of an inadequate circulation in the muscle groups involved in the cramps. Actual tightening of the muscle can be seen and felt. Unlike Sudeck's atrophy, evidence of sympathetic overactivity or of circulatory impairment may be absent or less striking in these cases and there is generally no osteoporosis.

A typical example of this type of reflex sympathetic dystrophy was encountered in a thirty-eight year old naval officer who had had a herniated nucleus pulposus removed, with relief of severe sciatic pain. Subsequently he developed cramping pain in the calf muscles of the leg, previously the site of sciatic pain. These cramps occurred at night and after walking two or three blocks. Physiotherapy and cessation of smoking did not influence this complaint over a six-month period. Right lumbar novocain sympathetic block gave complete relief for twenty-four hours. Lumbar sympathectomy has been effective in relieving the cramps for one and one-half years. At no time was this extremity cyanotic or cold and there was no osteoporosis. Excessive sweating of the right foot had been noted on occasion.

Causalgia has been listed as a form of reflex sympathetic dystrophy. The chief characteristic of this disorder is constant burning pain in the involved extremity. The disorder may follow nerve, blood vessel or soft tissue injury. Various degrees of vasospasm may be present. Pain is the main component. It is aggravated by touch and relieved by keeping the hand cold and wet. Causalgia is mentioned only for the sake of completeness. While it is frequently relieved by sympathetic block or surgery, the mechanisms involved have not been worked out. However, one possible mechanism may be release of spasm of the arteries supplying the cords of the brachial or lumbosacral plexus or of the median or sciatic nerves. All of these structures possess an arterial supply made up of small arteries roughly comparable to digital arteries in

size. "Tingling," a form of hyperpathia to touch, was demonstrated by Sir Thomas Lewis to occur following interference with arterial supply to the nerves of the forearm and hand, and a "causalgia-like" syndrome has been observed in the lower extremities of patients in whom aneurysms of the abdominal aorta have been wired, and in whom the procedure has resulted in definite impairment in blood flow to the lower extremities. It would seem that the hyperpathia and constant burning pain were due to a conduction defect over the involved peripheral nerve or plexus and that release of vasospasm or improvement in collateral supply may often restore normal conduction with the relief of pain symptoms.

It might also be pointed out that oscillographic readings may not be appreciably altered in causalgia or other vasospastic states. Oscillographic excursions are derived from pulses in large arteries, the walls of which consist of a relatively large adventitial layer and proportionately small, smooth muscle coat so that even the most intense vasospasm could not result in collapse of the vessel or total obliteration of its lumen. Arteries such as the radial at the wrist, the digital arteries or the artery of the sciatic nerves have a greater proportion of smooth muscle and less fibrous tissue in relation to the diameter of the lumen, and when these vessels go into spasm the lumen may be almost completely obliterated. This may well be one reason why the vasospastic features of Raynaud's syndrome involve the digits, and why in causalgia one would not obtain significant changes in oscillographic readings.

Chronic ulceration of the lower extremities is most often seen as a result of circulatory impairment frequently secondary to deep vein occlusion and associated with varicose veins. In such cases the foot distal to the ulceration is moist, cool and cyanotic. Trophic ulceration secondary to cord or peripheral nerve injuries is accompanied less often by these vasospastic changes.

A fifty-eight year old retired naval chief was admitted with a large, chronic cutane-

ous ulcer located just above the medial malleolus of the right foot. The lesion was 3 inches in size with a base of infected, pale granulating tissue and slough. Arterial pulsations were present in the right dorsalis pedis but absent over the posterior tibial artery. There were extreme varicosities of both legs. The right foot distal to the ulceration ached and was cyanotic, cold and moist. With conservative measures, the ulcer became slightly larger over a period of six weeks. The right foot became warmer after a lumbar novocain sympathetic block. Four weeks after right lumbar sympathectomy the ulcer had healed.

These cases may be considered to be a form of reflex sympathetic dystrophy in which the stimulus for the vasomotor reflex arises in the skin lesion, or they may be a form of local vasoconstriction due to humoral or toxic effects from a chronically infected superficial lesion.

Thromboangiitis obliterans (Buerger's disease) and arteriosclerosis are the most frequently encountered types of peripheral vascular diseases occurring in our clinic population. For the most part there is little or no vasospasm in such disorders. When arteriosclerosis is complicated by diabetes, vasospasm practically never exists. The major peripheral vessels are involved; accordingly, vessel pulsations, as determined by palpation or oscillometry, are depressed or absent. Attempts to improve circulation by sympathetic block are frequently unsuccessful. However, upon occasion (about 10 per cent of the cases) there is a striking degree of vasospasm. Such patients usually have aggravation of their intermittent claudication on exposure to cold, feel better in a warm environment and can increase their activity after interruption of the sympathetic outflow.

A sixty-three year old man in the Vascular Clinic with the complaint of cramping pain occurring in one leg after walking five blocks, is being studied. His pain is relieved by standing still for one minute. There was a history of myocardial infarction. All peripheral vessels were thickened.

Pulsations over the foot arteries were absent. Calcification of the arteries of both legs was extensive, as shown by x-ray. Following right lumbar novocain block, there was a rise of 4°C. in skin temperature over the toes. For four weeks after this block the patient doubled his walking tolerance; the pain was less intense when it appeared and the pain was relieved by standing for a few seconds. Subsequently he lost this good response and returned to his preblock state. There was no change in oscillometric readings at any time during this period. Incidentally, this is the longest effect we have observed to follow one novocain block.

DR. EDMUND N. GOODMAN: At St. Albans Naval Hospital we have had opportunity to observe many patients with thromboangiitis obliterans. It is our opinion that many of these patients have increased vascular tone and can be significantly improved by sympathectomy. Nineteen patients so treated have remained greatly improved for a period of two years.

STUDENT: What about morbidity and mortality in the various types of sympathectomy and procaine blocks?

DR. BRIDGES: Thoracic and lumbar sympathectomies carry no mortality. These patients may anticipate hospitalization of two to three weeks. They may expect to return to work two to three weeks after operation.

Procaine blocks have been reported to have resulted (rarely) in unexpected demise during the block. Whether these accidents are due to procaine sensitivity or to inadvertent injection into an artery or vein is often difficult to determine from the reports given.

Procaine block of the stellate ganglion may be followed, on occasion, by pneumothorax. This is generally small, producing pain as the only symptom. When extensive, hospitalization and aspiration of the air may be required.

DR. HEATH: Many patients with vasospastic phenomena have been noted to exhibit neurotic personality traits. It there-

fore seems proper to inquire into the psychologic mechanisms of vasospasm. Dr. Daniels will present the general psychosomatic approach to these diseases.

DR. GEORGE E. DANIELS: It is hardly necessary to point out that peripheral vascular changes occur in relation to emotion. We continually see evidence of this in the blush of embarrassment, the flush of anger or the blanching from fear. Clinical and experimental studies show that under such states of emotion internal organs, as well as exposed parts of the body and the limbs, show similar vascular changes. The subject with a permanent gastric fistula reported by Wolff and Wolf⁴ reflected parallel simultaneous changes in his face and gastric mucosa.

The best documented evidence of changes in peripheral circulation due to emotional changes has been gathered by Mittelman and Wolff.⁵ Under carefully controlled conditions 203 observations were made on forty-seven subjects, nineteen males and twenty-eight females. For some of the subjects an experimental situation was set up through the discussion of distressing life situations, reading of moving literature or requiring the patient to solve difficult problems under pressure. Other subjects were followed continuously during psychotherapy and circulatory changes in response to spontaneous emotional productions were registered. With both experimental and psychotherapeutic approaches, there was an immediate drop in skin temperature, reaching a maximum in some subjects of 13°C. whenever the subjects were placed in a distressing situation. Although great variations were observed in the different subjects, changes were constant for any one individual. In the entire series of experiments there were only three exceptions occurring in two subjects.

Mittelman and Wolff found essentially

no difference in the skin reaction of the patient with Raynaud's disease as compared with that of the other subjects except that the Raynaud patients showed blanching, pain and ulceration in the presence of lowered temperature. They found, as has been observed by others, that neither lowered temperature alone nor emotion alone produces these severe symptoms. A combination of the two is necessary. This has important implications for psychotherapy as well as for general medical management of such cases.

In the Raynaud patients who had undergone sympathectomy there were no local changes in relation to emotion. Surgery in such cases must be considered palliative and cannot be expected to change the personality aspect of the fundamental problem. Registration and discharge of tension, having been cut off through one route, may appear as a disturbance elsewhere. This was illustrated in a patient with Raynaud's disease who following sympathectomy developed a peptic ulcer. In many cases of this condition, before the final appearance of severe symptoms, there is evidence of a long history of emotional conflict. Raynaud, in his original article (1874), correctly appraised the situation: "In the present state of our knowledge, local asphyxia of the extremities ought to be considered as a neurosis, characterized by enormous exaggeration of the excito-motor energy of the gray parts of the spinal cord which control the vasomotor innervation."

Psychiatric treatment of patients with Raynaud's disease is often indicated, particularly in the early stages. The patient generally gives a history of early rejection by the family, with consequent basic insecurity, particularly in the face of crises. With psychotherapy, these patients often show direct registration of their return of confidence and feeling of support by a sensation of warmth in the extremities as contrasted with the shunting off of the circulation during periods of emotional withdrawal. The emotional component of Raynaud's disease should be evaluated

⁴ WOLFF, H. G. and WOLF, S. G. *Human Gastric Function*. London, 1947.

⁵ MITTELMANN, B. and WOLFF, H. G. Affective states and skin temperature: experimental study of subjects with "cold hands" and Raynaud's syndrome. *Psychosom. Med.*, 1: 271-292, 1939.

as a part of any thorough work-up. The severity and chronicity of the condition deserve a trial at psychotherapy if there is indication of an associated conflict.

Such conditions as Buerger's disease and diabetic atheromatosis have not been sufficiently studied to determine whether emotional factors play any part. If so, this presumably would be reinforcing a primary organic disease. Trench foot in the last war and traumatic arteriospasm in this war appear to be related to the reaction of certain constitutions under emotional stress plus injury to the part. In a recent article by Foisie⁶ the presence of tension states associated with arteriospasm was postulated as a likely explanation of the disproportion between severity of the reaction and superficiality of the wound. The severity and destructiveness of the reactions, once under way, would indicate that preventive psychotherapeutic measures, applied as early as possible, might be very worth while.

DR. ISIDORE MUFSON: In connection with Dr. Danicls' remarks concerning the interplay of emotional forces and peripheral blood flow we have been using radioactive tracers to study these interesting phenomena. We also find that the mere discussion of a distressing life situation causes vasospasm and a drop in the temperature of the skin. It requires no great imagination to recognize that during the patient's actual experience of these same situations an even greater vasospasm and drop in temperature may be produced. Since these psychologic disturbances are chronic, their total effect is equal to the results of a single experiment multiplied by the time factor. This prolonged vasospasm causes cumulative injury, often irreversible, to the tissues.

These mechanisms operate in Raynaud's disease because it has been shown that the entire disturbance can be reversed by breaking the psychosomatic chain present in these patients. There is evidence that scleroderma is a more advanced manifestation of Raynaud's disease. This is based on

the fact that in both diseases there is striking uniformity in the time relationship between the development of clinical manifestations and incidents in the life situation which are a threat to security. The intensity of this interaction is dependent upon a defect in personality. In the subject who is unable to integrate his problems fear stimulates the sympathetic pathways and thereby the smooth muscles of his minute vessels. If there is no resolution, chronic vasospasm persists.

The interplay of emotional forces and blood flow has been repeatedly observed in our clinic, and in many patients upon whom sympathectomy has been performed it has been found that progression of the process is not averted unless we can resolve the basic psychologic disturbance.

DR. HEATH: Turning now to management of peripheral vascular diseases, there are very few substances which have not been used in the therapy of organic peripheral vascular disease. None are very successful. On the other hand, the therapy of vasospasm is rational and usually highly effective. Procaine nerve block and preganglionic sympathectomy when well chosen are time-tested and proven procedures. Dr. Bridges will discuss them in some detail.

DR. BRIDGES: Dilatation of the blood vessels of the arm and leg may be accomplished by inhibition of the vasoconstrictor activity of the sympathetic or autonomic nerves. The sympathetic outflow to the upper extremity leaves the spinal cord (as a portion of the anterior root) from the second thoracic segment to as low as the eighth thoracic segment. The outflow to the lower extremity is from the thoracolumbar cord, specifically lumbar through up to the fifth thoracic segment. From each of these anterior roots a white ramus communicantes passes to the corresponding sympathetic ganglia. The postganglionic connections are grey rami to the spinal nerve or to adjacent blood vessels or to the sympathetic trunk.

Accordingly, one may paralyze sympathetic activity by spinal anesthesia or by novocain infiltration into the extradural

⁶ FOISIE, P. S. Traumatic arterial vasospasm, *New England J. Med.*, 237, 295, 302, 1947.

space. In these instances the conduction of efferent vasoconstrictor impulses over the anterior roots is impaired, either intradurally or extradurally. If low spinal anesthesia is used, only the legs will show evidence of vasodilatation; if the anesthesia extends to the upper thoracic segments, the arm will also partake of this vasodilatation response.

Inhibition of vasoconstriction impulses to the arm or leg may be obtained by interruption of these impulses at one of two regions of the sympathetic chain itself. All of the impulses passing to the upper extremity reach the inferior cervical and first and second thoracic ganglia, and from these ganglia postganglionic fibers go to the major vessels or to the brachial plexus. Accordingly, novocain infiltration of the inferior cervical and first thoracic ganglia (so-called stellate ganglion) will release the vessels of the corresponding upper extremity of vasoconstrictor control. The lower extremity vessels will dilate when novocain is infiltrated about the third lumbar ganglia through which the preganglionic fibers intended for the lower extremity make their connection with the postganglionic fibers to vessels and the lumbosacral plexus. Distal to the sympathetic trunk the vasomotor nerves are too scattered to allow as complete inhibition of vasoconstriction although vasodilatation will follow division or novocain block of major peripheral nerves which carry a portion of the vasoconstrictor fibers through the extremity. The median and ulnar nerves are most commonly selected when one desires to produce vasodilatation in the hand by peripheral nerve block. The posterior tibial nerve is most readily blocked to cause vasodilatation in the foot.

In summary, there are three sites at which vasoconstrictor nerve fibers to the extremities may be blocked—the anterior roots by spinal anesthesia, the sympathetic trunk and the peripheral nerves. Of these sites the sympathetic trunk lends itself best to novocain block, alcohol block or surgical approach.

Novocain block of the sympathetic out-

flow to the upper or lower extremity is a relatively simple procedure which can be performed in the clinic. Stellate ganglion block will produce vasodilatation in the arm. About 5 cc. of 2 per cent novocain is deposited along the body of the first thoracic vertebra. The needle is inserted just above the clavicle within its medial third and directed inward, backward and slightly upward to strike the body of the first thoracic vertebra. The novocain diffuses readily in the paravertebral space so as to bathe the stellate and second thoracic ganglia.

Success in infiltrating the stellate ganglion is indicated by Horner's syndrome, that is, the production of a small pupil, lid drop and apparent enophthalmos on the side of the injected ganglion. The face will become dry and pink. The homolateral upper extremity will show in chronologic order dilatation of superficial veins of the hand and forearm, dryness of the skin of the entire upper extremity and lastly the hand and forearm will become pink and warm. In the presence of a non-obstructed, normal vascular supply the skin temperature rise will exceed 5°C. Generally fifteen to thirty minutes will elapse before the full effect of the parasympathetic novocain infiltration has developed.

In similar fashion vasodilatation in the lower extremity will appear after lumbar novocain sympathetic block. It is possible to produce a high degree of vasodilatation by injecting 5 cc. of 2 per cent novocain close to the third lumbar ganglion which lies opposite the anterolateral aspect of the body of the third lumbar vertebra. Because of the difficulty of accurately placing a needle tip at this point, either two or four needles are used; they are inserted opposite the first and third ganglia or the first, second, third and fourth ganglia. The needle insertion is started at a point on the skin 5 cm. lateral to the corresponding spinous process. The transverse process is located and the needle point then directed just above the process and in an inward and medial direction to strike the lumbar verte-

bral body. This will be encountered at a depth of two and one-half finger-breadths beyond the depth of the transverse process. The novocain solution is deposited as close to the vertebral body as possible. It will diffuse through the paravertebral areolar tissue along the lumbar sympathetic chain for a variable distance.

Evidence of a successful block, in the lower extremity consists of dilated superficial veins, dry skin due to diminished sweat gland activity and a pink, warm foot and lower leg, appearing in this sequence. Evidence of increased blood flow or vasodilatation after a novocain block is found in the increased skin temperature and the reddish-pink color, in the dilated veins, and may be detected by plethysmographic observation, thermostromuhr readings and, more recently, by a heightened curve of radioactive sodium diffusion.

Novocain sympathetic blocks are used both as diagnostic and as therapeutic procedures. Regardless of the type of peripheral vascular disease if there is a rise of skin temperature of the digits of the involved extremity equal or greater than 3°C ., one may anticipate improvement of the disease or abatement of symptoms following removal of vasoconstrictor control. This would warrant the use of repeated novocain blocks or of surgical interruption of the autonomic system. On occasion a novocain block may produce marked improvement in symptoms although the skin temperature increase equals only 1 or 2°C . Repeated novocain blocks are in order rather than surgical sympathectomy, at least until a number of such blocks has consistently yielded symptomatic improvement.

Surgical sympathectomy of the upper or lower extremity is not a formidable procedure. The mortality rate should approximate zero and morbidity due to the operation should be of less than ten days' duration.

In each instance preganglionic types of sympathectomy are indicated. Due to the technical difficulty of resecting the fourth and fifth lumbar sympathetic ganglia, lumbar sympathectomies have always been

preganglionic sympathectomies. To denervate the foot and lower leg, the second and third, or upper three lumbar ganglia are resected through a flank or lateral abdominal, retroperitoneal approach.

The maximum rise in skin temperature will occur in the toes and foot. In the intact normal individual there is a temperature gradient from the thigh to the toes, the lowest temperature being that of the toes. After sympathectomy the gradient is largely lost and the temperature of the toes tends to equal that of the thigh. In the presence of marked occlusive vascular disease this gradient persists after sympathetic block or sympathectomy, as the rise of surface temperature is correlated with an increase in blood flow through the extremity.

Preganglionic thoracic sympathectomy to improve blood flow to the arm is carried out through a paravertebral incision with removal of a 2 inch segment of the medial end of the rib and its articulating transverse process. The third, or second and third ribs are so resected. The second and third thoracic roots are divided proximal to the dorsal root ganglia. The thoracic sympathetic chain is divided below the third thoracic ganglia. The sympathetic trunk between the stellate, second and third thoracic ganglia is carefully preserved, allowing preservation of the postganglionic connections from their ganglia to the brachial nerves and arteries thereby producing a preganglionic type of thoracic sympathectomy.

The reason for insisting upon preganglionic sympathectomy is that after total ganglionectomy or postganglionic sympathectomy the vessels become ten times more sensitive to circulating adrenalin which nullifies the effect of removing vasoconstrictor neural connections. After preganglionic sympathectomy the arteries are about three times as sensitive to circulating adrenalin, but this is more than compensated for by the removal of neural vasoconstrictor control.

DOCTOR: How permanent is the relief of vasospasm after sympathectomy? I have

heard that in a few years patients with Raynaud's disease, for example, may have a recurrence of their spasm due to increased sensitivity of the denervated smooth muscle to adrenalin.

DR. BRIDGES: The duration of vasodilatation following sympathectomy is unknown, and apparently variable. If the underlying disease is essentially occlusive, return of symptoms is almost certain. Raynaud's patients who have been seen in this Clinic after sympathectomy with symptoms, generally have symptoms related to non-sympathectomized regions. In many patients the impact of the vasospastic state remains limited to the sympathectomized area, and in these cases vasodilatation and relief of symptoms has persisted for two to five years. I know of no longer follow-up series than of five years' duration.

The relation of adrenalin sensitivity to return of symptoms has been suggested, but other factors may well be more significant as indicated by the observation of progressive symptoms in non-sympathectomized regions as well as in sympathectomized parts in a small group of progressive and ultimately fatal cases of Raynaud's disease.

DR. HEATH: Recently two new approaches to the therapy of vasospasm have appeared. At the University of Michigan the development and clinical application of the tetraethylammonium ion as an autonomic blocking agent has been reported.⁷ Certain sympatholytic agents have also been introduced. Dr. Gilman will discuss these.

DR. ALFRED GILMAN: Interest in the possible contribution of drugs to the problems of peripheral vascular disease has been stimulated by recent studies of drugs capable of blocking the effects of sympathetic nerve impulses. The two most promising agents are the tetraethylammonium ion and dibenamine. Their pharmacologic actions and therapeutic potentialities can best be appreciated by discussing them against the

background of the theory of chemical mediation of the nerve impulse.

In brief, this theory states that postganglionic autonomic nerves release at their endings chemical substances which stimulate the effector cells. Postganglionic sympathetic nerves, with a few exceptions, release sympathin, a substance which probably closely resembles epinephrine in chemical structure. Postganglionic parasympathetic nerves release acetylcholine. The term adrenergic and cholinergic nerves are employed to designate the chemical mediator. The theory of chemical mediation, although originally applied to account for the stimulation of autonomic effector cells by postganglionic autonomic nerves, has become much broader in scope. Thus, there is a large body of evidence to indicate that chemical mediators are involved in synaptic transmission in autonomic ganglia and at the junction between motor nerves and striate muscle. In both these instances the chemical mediator is acetylcholine. Thus, both sympathetic and parasympathetic preganglionic nerves and motor nerves to skeletal muscle may be termed cholinergic.

Although there has been considerable reluctance on the part of many neurophysiologists to accept completely the theory of chemical mediation, there is strong evidence in its favor. Moreover, it affords a reasonable interpretation for the action of drugs. Thus, autonomic blockade can be accomplished by chemical agents which prevent the chemical mediator from combining with the receptor substance of the effector cell. Atropine is an outstanding example of a drug which blocks the effects of acetylcholine released from postganglionic cholinergic nerves. Blocking agents are rather specific in their action. For example, atropine does not prevent the action of acetylcholine on striate muscle; this is accomplished, however, by the alkaloids of curare. The recent investigations of Acheson and co-workers have demonstrated that the tetraethylammonium ion establishes a blockade at autonomic ganglia. In other words,

⁷ LYONS, R. H., ET AL. The effects of blockade of the autonomic ganglia in man with tetraethyl ammonium. *Am. J. M. Sc.*, 213: 315, 1947.

although acetylcholine is released at the terminations of the preganglionic fibers, in the presence of the tetraethylammonium ion the ganglion cell remains unaffected and no postganglionic impulse follows preganglionic stimulation.

The pharmacologic actions of the tetraethylammonium ion are those to be expected from a functional autonomic denervation at a ganglionic site affecting both adrenergic and cholinergic postganglionic nerves. For example, the pupil assumes a neutral position and no longer responds to light. Motor activity of the gastrointestinal tract is greatly decreased, micturition is impaired, etc. Pertinent to the present discussion is the fact that adrenergic vasoconstrictor fibers are blocked. Peripheral resistance is decreased and peripheral blood flow increased. Compensatory vasomotor reflexes are lost and postural hypotension develops. However, it is obvious that the therapeutic usefulness of the tetraethylammonium ion is limited because of the ubiquitous effects of a blocking agent acting at a ganglionic site. Furthermore, the drug is rapidly excreted and its effects are of relatively short duration.

Although there are numerous drugs effective in blocking postganglionic cholinergic nerve impulses, there is a dearth of agents capable of adrenergic blockade. Those available in the past have been non-specific in their actions and have been much too toxic for therapeutic use. Interest in sympatholytic drugs has been greatly stimulated by the investigations of Nickerson and Goodman on the efficacy of dibenzylbetachloroethylamine (dibenzamine) to block selectively the effects of epinephrine and adrenergic nerve stimulation. Not only is the compound capable of effecting a functional sympathetic denervation but the actions are long-lasting, being measured in periods of days. Furthermore, although the compound possesses toxic side actions, Hecht and Anderson have demonstrated that adrenergic blockade can be accomplished in humans. Again the pharmacologic actions can be anticipated if one keeps in

mind that all of the known adrenolytic and sympatholytic drugs block only the excitatory and not the inhibitory effects of epinephrine and sympathetic nerve stimulation. Thus, there are no effects on the smooth muscle of the bowel and the bronchial tree. However, miosis occurs and the excitatory adrenergic impulses to the vascular bed are blocked. The vascular responses are similar to those elicited by the tetraethylammonium ion but in the case of dibenzamine actual reversal may occur due to the fact that the inhibitory effect of epinephrine on blood vessels may be unmasked. For example, the blood pressure may fall in response to the injection of epinephrine. Similarly the cold pressor test or brief periods of anoxia may cause a fall rather than a rise in blood pressure.

The therapeutic applications of dibenzamine are yet to be adequately defined. There is the real possibility that the toxic side actions of the compound may be greatly attenuated in one of its congeners. Surely this group of compounds will afford investigators in the field of vascular disease valued research tools and perhaps effective therapeutic agents.

DOCTOR: The reports on the therapeutic value of tetraethylammonium chloride in peripheral vascular diseases are conflicting. What are your views?

DR. HEATH: The use of the tetraethylammonium ion therapeutically has not produced satisfactory results. Two properties of the compound seem to be responsible for this. In the first place, the substance is rapidly excreted in the urine so that any effect is necessarily temporary. We have not observed prolonged remission of vasospasm even with repeated daily exhibition of the drug. This is contrary to other published results. Second, the effect of the substance is widespread upon all cholinergic synapses although the autonomic ganglia are most sensitive; therefore, selective vasodilatation cannot be obtained. This may be important in instances of occlusive disease in an extremity where generalized vasodilatation may result in an

actual decrease in available blood to the diseased area.

Sympathetic or adrenergic blocking agents such as the benzodioxanes, dibenamine (benzyl- β -chloroethylamine) and priscol (benzylimidazolines) certainly lack specificity and may present other objections to their use. In addition the benzodioxanes, for example, directly stimulate the smooth muscle of blood vessels while producing adrenergic (933 F) or both adrenergic and sympathetic (883 F) stimulation. Dibenamine blocks adrenergic effects on smooth muscle and does not directly stimulate the muscle but, as Dr. Gilman pointed out, is non-specific, long-acting and not an entirely benign substance. Priscol blocks adrenergic stimulation of smooth muscle and may dilate peripheral vessels directly but is uncertain in action and may have undesirable side effects.

At this clinic Dr. Mufson has been experimenting with the use of intra-arterial histamine and will briefly report on this method.

DR. ISIDORE MUFSON: An interesting aspect of therapy in peripheral vascular disease is the use of histamine in the relief of symptoms caused by obliterative endarteritis due to arteriosclerosis or angiitis. About two years ago we began to assay drug therapy of the peripheral vascular diseases by using radioactive sodium. We found that, as measured by the capacity to increase the diffusion rate of sodium, hypertonic saline and papaverine are practically inert whereas histamine by iontophoresis is a potent vasodilator. Histamine is not used by iontophoresis in endarteritis, however, because the insensitive skin of these patients is susceptible to electrical burns, but it can be given intravenously and so administered effectively reduces blood flow as judged by lowering of the radiosodium diffusion rate in the foot. It opens the healthy vessels of the upper half of the body at the expense of the diseased vessels of the legs. To fix histamine in the diseased arteries of the lower extremity histamine is given slowly by infusion from a

"pressure bottle" into the femoral artery so that very little escapes into the general circulation.

As the histamine enters the femoral artery a definite erythema spreads over the thigh from the groin to the knee, becoming more intense as the treatment continues. The back of the leg, then the front and finally the foot become pink. The extent and degree of the effect is variable. Patterns appear in pink and white which suggest the location and degree of the arterial blocks. The pale areas soon may become suffused as collaterals dilate under the influence of histamine. If the infusion is given too rapidly, histamine may escape into the general circulation and then the head and neck become very red while the foot is mottled and dusky. When the speed of flow is reduced, the foot becomes pink as the face again pales. A rise in skin temperature follows the erythema rapidly in the thigh and more slowly in the leg and foot; many patients show an increase of 6°C. in their toes. An erythema may be present with very little rise in temperature. The presence of both erythema and a rise in temperature over the skin of the calf indicates an increase in blood flow in the calf muscles which was found to be a *sine qua non* for relief of pain in the calf.

Figure 1 demonstrates that the diffusion of radiosodium after infusion of histamine is always greater in the calf and less so in the foot. This is to be expected because the block is more severe and collaterals less available in the foot. The superficial veins of the leg invariably become distended.

These effects represent a cross section of the immediate responses noted in a group of twenty-eight patients with endarteritis obliterans who had been receiving weekly intra-arterial infusions of as much as 1 mg. of histamine base in 500 cc. normal saline. No other treatment was used concurrently and each patient had a backlog of one or more types of treatment from nine months to five years.

To evaluate the efficacy of intra-arterial histamine infusions the criteria chosen were

the effect on two symptoms of arterial insufficiency in the lower extremities: first, walking tolerance, the number of city blocks a patient is able to walk before he is forced to stop by a cramp in the calf; second, sleep tolerance, the number of hours in bed before the patient is awakened by a cramp in the calf which forces him out of bed for relief.

There were three types of response in walking tolerance. A very good group consisted of nineteen patients. These began with a walking tolerance of from one to three blocks; after a series of weekly infusions they were able to walk from fifteen to twenty blocks without stopping. They have maintained this improvement often without further treatment. The good group totaling six patients attained between six and ten blocks from a low of one to two blocks. Monthly treatments were given to maintain this level. In the poor group of three patients no improvement appeared after six treatments, when they were discontinued. Sleep tolerance was improved in 100 per cent. In less than two to six treatments patients who could barely rest slept through the night. They were our most grateful patients.

The oscillometric readings, which were very low (0 to 1 in all except one patient) remained unchanged, showing that the major block persisted. In spite of this the treatment had developed an efficient collateral circulation or at least had made it available. Why such a durable and competent collateral circulation should develop after this treatment is not altogether clear. Histamine is a potent vasodilator, at least as effective as sympathectomy by block or section in the presence of an obliterative endarteritis, as judged by production of erythema, rise in skin temperature and rise in radiosodium diffusion curve. We surmise that the direct effect of histamine does not last longer than six hours although the record of the results suggests that vasospasm has been permanently reversed. Analysis of the problem may give the reason. To begin with a primary force such as the

degenerative process initiates a block in one or more arteries. The collaterals are available but cannot take over the burden because they are in reflex spasm as a result of the original block and its attendant distress. Some patients are helped by resting for six weeks or more because the collaterals open spontaneously. The patients whom we treated did not develop adequate collateral circulation spontaneously but apparently did so after administration of histamine.

Success in the treatment of patients with histamine rests not alone on the presence and availability of a competent collateral circulation but also on the absence of a cause for persistent reflex and histamine-resistant vasospasm of these same collaterals. It is advantageous to have a procedure which can be repeated as often as necessary to care for new problems as they arise, an advantage which sympathectomy does not possess.

SUMMARY

DR. HEATH: Our knowledge of the diseases of the peripheral blood vessels is small. Arteriosclerosis and thromboangiitis obliterans result from unknown causes so that definitive therapy is impossible. Somewhat more is known about the factors governing vasoconstrictor tone and vasospasm; in such conditions a mechanism is often discernible even though incompletely understood. Nevertheless, it is upon this knowledge that the investigative and therapeutic approach to the problems of peripheral vascular disease is largely based, and it is clear that by interrupting the sympathetic supply either spasm or the normal vasoconstrictor tone can be considerably decreased often to therapeutic advantage.

Blood flow through an extremity is extremely variable depending upon temperature, emotion, physical activity and other body functions. Extensive arteriovenous shunting which takes place in the hand and the foot adds to the magnitude of these changes. Whereas considerable information may be gained about the state of peripheral flow by inspection and palpation,

which may be placed into objective qualitative terms by the use of skin temperature determinations, oscillometry and arteriography, resort must be had to the venous occlusion plethysmograph for quantitative information. Recently the use of adrenalin iontophoresis of the skin has made it possible to make approximate measurements of blood flow to muscle. As yet no adequate method exists to measure peripheral blood flow during any state except rest.

Examples of vasospastic disorders improved by sympathetic procaine block or sympathectomy are given and a detailed description of these procedures is included in the clinic. It should be emphasized that careful evaluation of the probable effects of sympathectomy by the initial use of a procaine block should be carried out before an operative procedure is undertaken.

Use of autonomic blocking agents such as tetraethylammonium chloride is at present restricted to diagnostic procedures since their action is widespread and temporary. Sympatholytic agents so far available are too uncertain for general use. It is to be hoped, however, that further progress along these lines may result in a more practical application of these principles.

The intra-arterial use of histamine appears to have a sound physiologic basis and in the hands of Dr. Mufson seems to produce good results. This is particularly true of cases in which no appreciable spasm has been demonstrable by nerve block and in which the chief complaint is intermittent claudication. If further experience confirms these early results, a valuable therapeutic approach will be available for a group of patients heretofore considered beyond aid.

Clinico-pathologic Conference

Pneumococcal Meningitis*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. M., (B. H. No. 156274), was a forty-eight year old white married tool sharpener who entered the Barnes Hospital on February 27, 1948. He was comatose on admission and never regained consciousness; the following brief history was obtained from his wife. The family history and past history were, as far as could be determined, non-contributory. The patient had been in good health until two weeks before entry when he first noted a sense of fullness in his left ear and his hearing became less acute on that side. Eight days later he developed pain in the ear and a physician was called; he gave the patient one injection of penicillin intramuscularly and similar injections on each of the following four days. The patient was told that he had an ear infection which had spread to his blood. Two days before entry he complained of a severe headache which became progressively worse and necessitated sedation. A few hours previous to admission he suddenly became stuporous and delirious and was brought to the Barnes Hospital.

On entry to the hospital physical examination revealed a temperature of 39°C., pulse 80, respirations 32 and blood pressure 140/80. The patient was thrashing about in delirium and would not respond to questions. He appeared well developed but rather thin. The skin was hot and dry but no eruption was seen. There was no lymphadenopathy. The pupils were round, regular and equal and reacted well to light. The eyegrounds appeared normal except for slight narrowing of the arterioles.

Examination of the left ear showed a small hematoma in the auditory canal. The drum was reddened, moderately scarred and retracted and the landmarks were not visible. The right ear was not remarkable. The nasal mucosa was red and dry and was covered with a small amount of mucopurulent discharge. The pharynx and tongue were likewise red and dry. Several of the teeth were carious. The neck was stiff; the neck veins were not distended and the trachea was in the midline. The thyroid could not be felt. Examination of the lungs revealed a few scattered ronchi bilaterally but no other abnormal findings. The heart was not enlarged; the rhythm was regular and the sounds were somewhat distant but there were no murmurs. Examination of the abdomen was negative. Neurologic examination revealed left divergent strabismus, although the external ocular muscles seemed intact, spasticity of all extremities, bilateral Babinski signs and questionable Kernig signs. A more detailed examination was not possible because of the patient's condition.

Admission laboratory findings were as follows: Blood count: red cells, 3,850,000; hemoglobin, 13 Gm.; white cells, 16,080; differential count: juvenile forms, 3 per cent; stab forms, 19 per cent; segmented forms, 68 per cent; lymphocytes, 15 per cent; monocytes 5 per cent. Urinalysis: albumin, 2+; sugar, 3+ (after intravenous glucose); acetone, 2+; sediment, occasional granular cast. Blood culture: negative.

Immediately after admission a lumbar puncture was performed. Manometric readings were not possible, but 10 cc. of cloudy

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

fluid were withdrawn. The fluid was not xanthochromic; it contained 8,600 white cells per cu. ml. with acid, and of these 93 per cent were polymorphonuclear leukocytes. On smear extracellular gram-positive diplococci were seen; these proved on typing to be type VII pneumococci. Culture of the spinal fluid also revealed type VII pneumococci. At the time of the lumbar puncture 15,000 units of penicillin were introduced intrathecally. The patient was given 200,000 units of penicillin intramuscularly and subsequently received 100,000 units every two hours. He was also given 2 Gm. of sulfadiazine in $\frac{1}{6}$ molar sodium lactate solution intravenously. He was seen by an otologic consultant who made a diagnosis of chronic left otitis media with possible brain abscess; he advised exploration of the mastoid cells as soon as the meningeal infection was better controlled. On the second hospital day a lumbar puncture was again performed and the spinal fluid was found to contain 20,000 white cells per cu. ml., of which 95 per cent were polymorphonuclear leukocytes. On smear, however, no organisms were seen and culture of the fluid was likewise negative. The patient's respirations became shallow and irregular and there were short periods of apnea. The breath sounds were almost inaudible. A bronchoscopy was performed but no evidence of bronchial obstruction was found. Soon thereafter there were convulsions localized to the left side of the face and these were followed by two generalized convulsions. Subsequently, intermittent twitching of the facial muscles was described. Roentgenograms of the sinuses and of the mastoid region showed no apparent abnormalities. A roentgenogram of the chest was not satisfactory.

On the second day the blood-sulfadiazine level was 10.6 mg. per cent and the patient was given 4 Gm. of sodium sulfadiazine in $\frac{1}{6}$ molar sodium lactate solution subcutaneously. After that infusion the sulfadiazine level rose to 13.2 mg. per cent. On the third hospital day the patient had a clonic convulsion which involved the left

side of his body; it lasted approximately thirty seconds. Neurologic examination at that time showed a left hemiplegia with diminished reflexes. On a later examination, however, the reflexes were slightly hyperactive. The left pupil was noted to be smaller than the right and was fixed. The patient remained comatose.

After consultation by a neurologic surgeon the patient was transferred to the Neurosurgical Service and ventriculograms were done. The ventricular fluid was cloudy and contained large particles of exudate. Approximately 30 cc. of air were injected. X-ray films showed that the ventricles were dilated but there was no lateral shift. The third ventricle was normal except for dilatation. Following ventriculography, the patient developed severe epileptiform convulsions. He was given sedatives and placed in an oxygen tent and given parenteral fluids. His respirations, which had been irregular and shallow, improved. Another spinal puncture was performed but the fluid was so thick that it would not flow and it had to be aspirated. Approximately 40 cc. were withdrawn and 50,000 units of penicillin were injected into the subarachnoid space. Following this procedure, mild convulsions occurred. On the fourth day the left ventricle was tapped and air and blood-tinged cerebrospinal fluid were removed. The fluid was apparently not under pressure. Forty thousand units of penicillin were instilled. Another lumbar puncture was performed and 50 cc. of very cloudy fluid, filled with shreds of thick mucoid particles, were obtained. Irrigation was carried through the needle and 50,000 units of penicillin were injected. Simultaneously 50,000 units of penicillin were introduced into the right ventricle. The patient was obtunded and his respirations were of the Cheyne-Stokes type. Because of urinary incontinence, a retention catheter was inserted.

At this time another roentgenogram of the mastoids revealed the right to be normal but in the left there was increased density throughout the structure anterior to the

sinus plate. A large portion of the cell outline in that region could not be visualized and those cells which were seen were indistinct. A diagnosis of left mastoiditis was made. Following these studies, a left mastoidectomy was performed. The antrum was entered with a perforating burr and a small amount of pus escaped. The mastoid cells were extenterated. They appeared relatively normal except that the bone about the tegmental plate over the dura was somewhat soft; it came away easily exposing normal dura which did not bulge. The left lateral sinus was uncapped and appeared normal. The dura was removed back to the sinus which also appeared normal. The posterior mastoid sinus cells were normal. The incus was exposed but was left intact.

On the fourth day the temperature spiked to 41.8°C. from a level which had varied between 39 and 40°C. During the previous twenty-four hours the patient had received 100,000 units of penicillin intraventricularly, 100,000 units intrathecally and 800,000 units intramuscularly. He had likewise received 6 Gm. of sodium sulfadiazine, 1,000 cc. of lactate Ringer's solution, 2,000 cc. of $\frac{1}{6}$ molar sodium lactate and 500 cc. of whole blood. On the fifth hospital day an attempt to enter the right ventricle was unsuccessful. The left ventricle was easily penetrated. Moderately bloody fluid was obtained which was not under pressure. Fifty thousand units of penicillin were instilled. A lumbar puncture was performed; the fluid at first had much exudate and was markedly cloudy. The cell count was 65,000; most of the cells were polymorphonuclear leukocytes. Fifty thousand units of penicillin were introduced. During the course of the day the patient had frequent brief convulsions during which he stopped breathing. His eyes were noted to turn to the left.

On the sixth hospital day painful stimuli elicited some response on the part of the patient. A lumbar puncture at this time revealed an initial pressure of 200 mm. of water and a final pressure of 150 mm. of water after removal of 25 cc. of fluid. The

fluid appeared clearer and contained less sediment. The cell count was only 12,030. Later in the same day the patient had several more convulsions, each of which lasted about one minute. Although they were generalized, they were more marked on the left. Laboratory studies on the sixth day revealed the red count to be 3,210,000; hemoglobin, 13 Gm.; the white cell count was 8,800 with 35 per cent stab forms, 46 segmented forms and 19 per cent lymphocytes. The blood protein nitrogen was 21 mg. per cent and the blood sugar 114 mg. per cent. During this hospital stay the patient had repeated cultures of both ventricular and lumbar cerebrospinal fluid and all of these, except for the first one noted, were sterile. His temperature ranged between 39 and 40°C., except for occasional spikes. Shortly after one of his generalized convulsions on the sixth hospital day, March 4, 1948, the patient expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Dr. Bottom, would you care to comment on the x-ray films?

DR. DONALD S. BOTTOM: Films of the skull were attempted but only a lateral view could be taken and no remarkable findings were noted. Ventriculograms showed filling of both lateral ventricles and some air in the third ventricle. Although the ventricles were slightly dilated, they were in normal position and one would conclude that there was a block of the ventricular system distal to the third ventricle. The chest film was very poor but there was a suggestion of patchy infiltration throughout both lungs.

DR. ALEXANDER: This case is one of type VII pneumococcus infection of the leptomeninges and affords us an excellent occasion to discuss the modern methods of treatment of this disease. Before proceeding with the discussion of treatment, however, let us ask Dr. Harford to discuss this particular organism and tell us something of the route by which it may gain access to the meninges.

DR. CARL G. HARFORD: The type VII pneumococcus is one of the more common causes of pneumococcal pneumonia being responsible for approximately 6.5 per cent of all cases in a large series. It ranks next to types I, II, III and V in frequency of occurrence and is thus an important human pathogen. It is thought that infection due to the pneumococcus, whether it be pneumonia or meningitis, arises as a result of transmission of the organism from a carrier to a susceptible individual. Approximately 1 per cent of the population carries the type VII pneumococcus; this rate is rather low as is also the case with types I and II. One can postulate that when a patient develops an upper respiratory infection, perhaps due to a virus, secondary infection with the pneumococcus ensues. Probably in the case we are discussing the patient had a respiratory infection and then came in contact with an individual who carried type VII pneumococci. How he actually acquired the organism is a matter of conjecture although certainly inhalation of droplets, as a result of exposure to a cough or a sneeze, is quite possible.

DR. ALEXANDER: For how long are these organisms viable in dust? Could the patient have inhaled air-borne organisms?

DR. HARFORD: Yes, it has been shown that pneumococci are present in the dust of rooms in which carriers have been present.

DR. ALEXANDER: I believe certain studies have indicated that the organisms may persist for many days. This patient had apparent difficulties with his ear but when at operation the mastoid cells were exposed, they were not remarkably involved and when the dura was uncapped no important findings were observed. Do these data in any way invalidate the idea that the patient may have developed the meningitis via the middle ear?

DR. HARFORD: I do not think so. The pneumococcus has a reputation for passing into the central nervous system without leaving much evidence behind regarding its pathway. I think this patient certainly had something wrong with his ear and the

chance of the ear having been the portal of entry seems to me to be excellent.

DR. ALEXANDER: By what other route may a patient acquire pneumococcal meningitis?

DR. HARFORD: Bacteremia arising in the course of lobar pneumonia may lead to meningitis.

DR. ALEXANDER: Would you comment on the relative incidence of pneumococcal and meningococcal meningitis?

DR. HARFORD: Meningococcus meningitis is more common during epidemic periods but in interepidemic periods the incidence of meningococcal and pneumococcal meningitis is about equal.

DR. W. BARRY WOOD, JR.: Sinus infection has not been mentioned as a portal of entry in pneumococcal meningitis. Would Dr. Harford comment on the incidence of pneumococcal meningitis following sinus infection?

DR. HARFORD: It certainly occurs but I cannot state the exact incidence.

DR. HENRY A. SCHROEDER: In regard to the rather unimpressive findings at the time of mastoidectomy it seems entirely conceivable that the intensive penicillin and sulfonamide therapy prior to operation had a definite effect on the infectious process so that when exploration was performed the findings were much less striking than they might have been originally.

DR. HARFORD: I think your point is very well taken.

DR. ALEXANDER: I would like Dr. Wood to discuss the problem of recovery from pneumococcal infections in general. Why is it, for example, that in untreated pneumococcal pneumonia the majority of patients recover whereas in untreated pneumococcal meningitis the mortality approaches 100 per cent?

DR. WOOD: I do not believe that your question can be answered completely, Dr. Alexander, but we may comment on some aspects of the problem. The anatomic structure of the lung is such that the defense mechanisms at that site, particularly those having to do with phagocytic cells, are

relatively efficient. It seems quite clear that the principal way in which the pneumococcus is destroyed in the body is by phagocytes, and the process of phagocytosis must therefore be studied if the mechanism of recovery is to be understood. The explanation for the efficiency with which phagocytes operate in the lung appears to relate to the tremendous surface area available to the leukocytes in this organ. The leukocytes utilize the extensive surfaces of the alveolar walls to destroy pneumococci by the mechanism of surface phagocytosis. When one contrasts the situation extant in the lung with that which obtains in an open cavity such as the pleural space or the subarachnoid space, it is apparent that the amount of surface available to the leukocytes is very small in the latter by comparison. Therefore the phagocytes in the meninges operate at a disadvantage since they have access to a relatively small area of tissue surface against which they can trap and thus phagocyte the encapsulated bacteria. As you have pointed out the case fatality rate when the pneumococcal infection involves the lung is relatively low, 20 to 30 per cent, whereas in the subarachnoid space it approaches 100 per cent.

DR. ALEXANDER: Is type specific antiserum given in an attempt to opsonize the organisms in pneumococcal meningitis?

DR. WOOD: Prior to the introduction of modern chemotherapeutic and antibiotic drugs, antiserum was the agent of choice in pneumococcal meningitis. When antibody is introduced into the subarachnoid space, the fatality rate is lowered somewhat but not to the degree that results from the use of penicillin. The antibacterial agents which stop the multiplication of the invading organisms are considerably more efficient than antiserum which does not affect multiplication but merely opsonizes the organisms and thus promotes phagocytosis.

DR. ALEXANDER: This patient received very large amounts of penicillin and although his general clinical condition progressively deteriorated and the spinal fluid

cell count rose, all cultures were consistently negative except the initial one. What inference can be drawn from these findings, Dr. Hagemann?

DR. PAUL O. HAGEMANN: One can certainly postulate that the organism was quite susceptible to penicillin. Had it not been so I believe the organism would certainly have been recovered in subsequent cultures. I should like to ask whether penicillinase was used in the culture media. In view of the large amounts of penicillin which this patient received it is conceivable that enough penicillin was carried over into the culture medium to inhibit growth of the organism *in vitro*.

DR. HARFORD: We do not use penicillinase routinely in our laboratory although we do employ it when indicated. I am sorry that I cannot remember whether it was used in the cultures in this instance. It might be pointed out, however, that if enough penicillin was carried in the spinal fluid to the culture medium to inactivate the growth of the organisms *in vitro* then it would probably be sufficient to do so *in vivo*. It must be remembered also that penicillin not only exerts a bacteriostatic action but also under certain conditions it is bactericidal. For example, *in vitro* .06 or .07 units of penicillin will kill a rapidly growing culture of pneumococci in five hours. The amounts given this patient would result, in the blood at least, in exceedingly high levels many many times those necessary to kill the organisms *in vitro*.

DR. ALEXANDER: As a result of the pathologic changes due to the meningitis is it not possible that penicillin did not reach many of the organisms in this case?

DR. HARFORD: It is well known that penicillin, when administered parenterally, does not reach the subarachnoid space in high concentrations. That observation has led most authorities to recommend that penicillin be given intrathecally in meningitis. Even intrathecal penicillin may not be effective if there is thick plastic exudate in the meninges.

DR. ALEXANDER: At staff rounds several weeks ago we had an excellent discussion concerning the use of intrathecal penicillin participated in by the neurosurgeons, otolaryngologists, neurologists and internists. There seemed to be evidence both in favor and against the introduction of large amounts of penicillin directly into the subarachnoid space.

DR. HARFORD: Penicillin when given intrathecally to normal individuals causes chemical meningitis. When a patient already has meningitis, however, it is very difficult to know whether the penicillin increases the degree of meningeal irritation. Usually the chemical effect is ignored in favor of active treatment of the infection.

DR. ALEXANDER: It would seem well to raise the question, in the case under discussion, as to whether the patient was cured by the original 15,000 units of penicillin which were introduced at the time of the first lumbar puncture and if so whether his subsequent unsatisfactory course could have been either partly or completely due to the large amount of penicillin subsequently given.

DR. WOOD: The problem raised is a most difficult one. As you have stated, Dr. Alexander, we have discussed it at great length with the neurologists and neurosurgeons and there is much difference of opinion. The neurosurgeons have had a great deal of experience in treating advanced cases of pneumococcal meningitis. Patients such as this one, admitted to the hospital after having been treated inadequately, do not respond to the usual therapeutic regimen and are then sent to the neurosurgical service for more heroic measures. Dr. Henry Schwartz has given a large number of these patients repeated doses of 50 or even 100,000 units intrathecally or intraventricularly. On the other hand, most internists, pediatricians and neurologists hesitate to use more than 20,000 units a day because of the irritative action of the drug itself. The pathology of this case should be extremely instructive and I am very anxious to hear Dr. Dam-

min's findings. There would appear to me to be three possibilities: First, it is possible that we did not control the meningitis due to the fact that there was so much exudate over the surface of the brain that the organisms in the fibrinous exudate were unaffected by the drug. Second, the infection may have been controlled by penicillin but the inflammatory reaction in the meninges may have progressed to the point where it caused mechanical block of the foramina of Luschka and Magendie. Third, it is conceivable that the penicillin itself produced a continual meningitis. If viable organisms were found at autopsy, the neurosurgeon's point of view will be supported, namely, that very large doses of penicillin should be given. If the persistent meningitis appears to be of chemical origin, then a more conservative approach will seem indicated.

DR. ALEXANDER: Dr. Bottom, do you believe that the ventriculograms are indicative of internal hydrocephalus?

DR. BOTTOM: The ventricles are not as dilated as one usually sees, but the findings suggest some delay in absorption of cerebrospinal fluid.

DR. JOHN R. SMITH: Dr. Wood, would you comment further on the possibility which you previously outlined, namely, that the inflammatory reaction persisted after the pneumococci were destroyed.

DR. WOOD: When there is a severe inflammatory reaction to infection, there is often a long period during which the inflammation persists after the infection has been brought under control. This phenomenon is most often seen in the lung where x-ray shadows of a pneumonic lesion may become larger after the crisis, indicating a lag in the clearing of the exudate. Thus, the continuation of the inflammatory response, despite the fact that the organisms have been killed, indicates that all the sources of irritation have not been removed. The death of the organisms and the release of toxic products of the many bacterial cells act to prolong the inflammation. If there were a large number of organisms in the sub-

arachnoid space in the present case and they were all killed, there might still be enough of a stimulus to cause the inflammatory response to persist for some time. However, the response apparently continued for four days after the cultures had become negative and this period would appear to one to be too long for such a mechanism to operate. I believe that the two most likely possibilities are that there was either persistent infection or that the continued meningitis was due to the penicillin.

DR. HENRY H. GRAHAM: I do not know the findings which Dr. Dammin will describe, but investigators studying this problem have found that they can produce a reaction with penicillin that is indistinguishable from infection as far as the fibrous reaction in the meninges is concerned. Thus, in this case, it may be impossible to make a distinction.

DR. ALEXANDER: May the reaction give rise to a polymorphonuclear exudate?

DR. GRAHAM: Yes.

DR. WOOD: I should like to comment further on the fibrin reaction. The deposition of fibrin constitutes a part of the host's mechanism of defense against infection, but the process may in the end be harmful. In this case a fibrinous exudate will probably be disclosed over the surface of the brain, particularly at the base. The same type of reaction occurs in the pleural space in empyema. Until the present time we have had no satisfactory method of attacking this problem and patients die or are disabled because of the purely mechanical effects of the organized fibrin. Recently at New York University Dr. Tillett has obtained in relatively pure form from hemolytic streptococci a fibrinolysin which he injects into the pleural space to destroy fibrin after it has been laid down as the result of an experimental infection. Whether his observations in experimental animals will lead to a practical form of therapy remains to be seen, but his findings are already of the greatest interest. The patient under discussion today was one in whom the injection of a fibrin-

olytic agent into the subarachnoid space to remove the fibrinous exudate might have been most helpful.

DR. ALEXANDER: Is the fibrinolysin specific for fibrin arising from any form of infection?

DR. WOOD: Streptococcal fibrinolysin will lyse fibrin of human blood regardless of the process that caused it to arise.

DR. ROBERT J. GLASER: The streptococcal fibrinolysin may be further defined. Beta-hemolytic streptococci produce an enzyme called streptokinase which activates a fibrinolytic system within the blood; that is, the enzymatic product of the streptococcus does not in itself lyse fibrin but activates a lytic agent that is present in normal serum.

DR. HAGEMANN: In my opinion this patient probably had persistent localized meningitis. He had infection with inadequate therapy for four days before coming to the hospital. Such an interval constitutes a very long time when one is dealing with pneumococcal meningitis. The neurologic signs were rather localized. He had chiefly left-sided manifestations which I interpret as arising from meningitis adjacent to the left mastoid. I think it would be unlikely for penicillin to give rise to a localized reaction.

DR. HARFORD: One further point should be made. It seems to me that the actual cell count in the spinal fluid may not be a satisfactory indication of the condition of the patient. It not infrequently happens that when the first lumbar puncture is performed, the fluid is turbid as a result of the large number of bacteria present. The following day when the culture may have become negative and the bacteria are gone the cell count may rise considerably as a result of the process already referred to by Dr. Wood.

DR. GRAHAM: Under even inadequate penicillin therapy the cell count may not return to normal but it usually decreases and the patient's symptoms often clear. He may even become ambulatory for a matter of days or even weeks, only subsequently to have a focus in the brain that has not

cleared completely reactivate the meningitis. Therefore, in this particular infection apparent clinical cure does not always indicate permanent freedom from difficulty.

DR. ALEXANDER: In summary, it seems clear that this patient had pneumococcal meningitis which prior to his admission to this hospital had progressed to a point where irreversible changes had developed. He received very large amounts of penicillin parenterally and into the cerebrospinal fluid itself, and it is possible that although the infection was eradicated the inflammatory process resulting from either the meningitis or from penicillin itself may have led to such a severe reaction as to cause death. The tragedy of a case such as this lies in the fact that had this patient been treated promptly and intensively on the first or even the second day of his illness he would undoubtedly have been cured of the infection.

Clinical Diagnoses: Pneumococcal meningitis, ? controlled; ? multiple abscesses in the meninges and brain; ? meningitis due to irritation (by penicillin).

PATHOLOGIC DISCUSSION

DR. ALFRED DECKER: External examination revealed a well developed, well nourished, white male appearing about his stated age of forty-eight. The body weighed 65 Kg. The head was shaved. There were bilateral surgical incisions in the parieto-occipital regions. There was a partially sutured surgical incision anterior to the upper portion of the left ear from which two rubber-dam drains and a rubber tube extruded. The left ear canal was packed with a wick which was blood-stained. There were numerous needle punctures in all extremities and over the lower lumbar spine. When the body was opened, there were 300 cc. of turbid fluid containing a few flecks of fibrin in the abdominal cavity. There was no apparent serosal reaction. There were 200 cc. of faintly turbid fluid in the right pleural cavity, 100 cc. of similar fluid in the left and 50 cc. of clear fluid in the pericardial sac. Both lobes of the left

lung were fixed by firm fibrous adhesions. The lungs weighed 1,350 Gm. and the dependent third of both lower lobes was dark red in color and nodular to palpation. There was no fresh fibrin on the pleural surfaces. On section the trachea and bronchi were seen to be filled with a white mucopurulent exudate. There were patchy areas in both lower lobes which presented the raised granular appearance of bronchopneumonia. The liver weighed 1,670 Gm., was dark red in color and on section revealed prominence of the central areas of the lobules. The right kidney weighed 190 Gm., the left 230 Gm.; both were dark and striations were dark colored and prominent. The other thoracic and abdominal viscera appeared grossly normal.

After removal of the brain examination of the dural sinuses revealed small thrombi, perhaps 7 mm. in their greatest diameter, in the posterior superior portions of both cavernous sinuses. These were loosely adherent, gray-pink in color and suggestive of antemortem thrombi. The dura over the left petrous ridge was slightly discolored. It was intact, however, and there was only minimal roughening of the cerebral surface. When the dura was stripped from this area, an operative defect was seen unroofing the mastoid air cells. This defect was filled with a firm hematoma without evidence of suppuration or bony involvement. In the left middle ear there was a drop of purulent fluid. The right petrous bone revealed extreme pneumatization with actual perforations of the bone subdurally but no evidence of inflammation in either the mastoid air cells or the middle ear. Examination of the brain revealed mucoid, yellow-white purulent material in the subarachnoid space over both cerebral hemispheres with concentration in the sulci and markedly predominant over the right frontal and parietal lobes. At the base of the brain there was similar exudate extending from the optic chiasm to the medulla and laterally over the anterior border of both cerebellar hemispheres. The areas of the foramina of Luschka bilaterally were matted



FIG. 1. Low power view of the dura from the mastoid area showing the inflammatory reaction on the cerebral surface.

FIG. 2. Another section of the area shown in Figure 1 under higher magnification. There is condensation of fibrin with much nuclear debris.

FIG. 3. Section from the right parietal area showing the dense collection of exudate.

FIG. 4. Higher power view of the section in Figure 3. Very few of the polymorphonuclear leukocytes are well preserved.

with thick yellow pus. Examination of the meningeal covering of the cistern revealed opacity but no frank exudate. Section of the brain revealed very slight dilatation of the ventricles and blunting of their outline with possibly 5 cc. of clotted blood in each. No exudate was demonstrable. The tracts of the ventricular punctures revealed considerable hemorrhage. Examination of the spinal cord revealed exudate over the dorsal aspect of the cord in the subarachnoid space from the cauda equina up to the mid-dorsal region. Cultures were made at the heart's blood, from the exudate over the cerebrum, and from the right lower lobe of the lung.

DR. GUSTAVE J. DAMMIN: We are dealing with a rather unique case which concerned not only the internist but also the neurologist, neurosurgeon and the otorhinolaryngologist. We have evidence that the patient had acute seropurulent otitis media on the

left with acute purulent mastoiditis, as reported by Dr. Walsh in his operative note, an area of pachymeningitis over the mastoid area and diffuse leptomeningitis more localized over the right cerebral hemisphere. There was no evidence of brain abscess or any other well circumscribed focus of infection. By gross examination we cannot accurately estimate the duration of these lesions and the duration of each lesion will influence our speculation regarding the sequence of events.

The lesion over the mastoid involved a small area. Figure 1 shows a low power view of the dura from the mastoid area with an inflammatory reaction on the cerebral surface. The peripheral portion consists of a loosely constructed fibrin reticulum and the cells within it are well preserved, but if one examines the deeper portion under higher power (Fig. 2), one finds a condensation

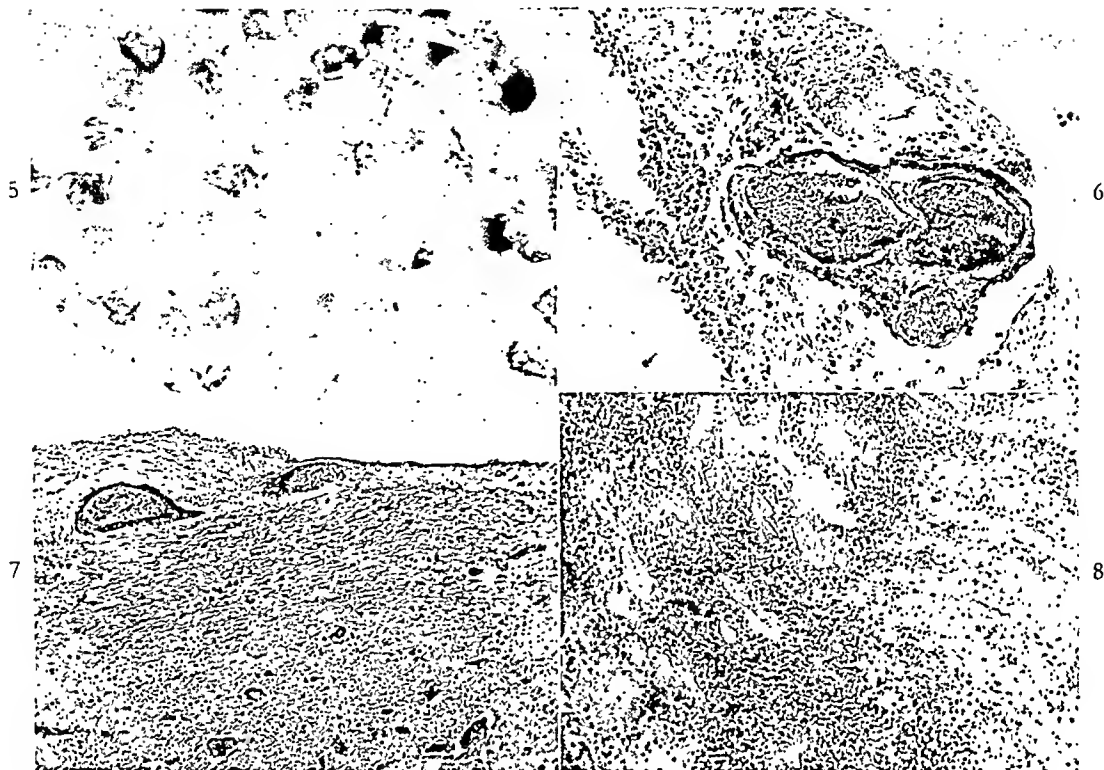


FIG. 5. Section of the exudate over the right parietal lobe showing organisms which morphologically resemble pneumococci.

FIG. 6. A section of the choroid plexus to show the inflammatory reaction.

FIG. 7. Section showing perivascular collection of cells adjacent to the ventricles.

FIG. 8. Section of one of the thrombi removed from the cavernous sinus. Note the presence of platelet columns.

of fibrin with much nuclear debris, suggesting a process at least several days old. The patient was operated upon on March 2nd and died on March 4th. The deeper portion of the process appeared to be more than two days old. I believe we can assume that it represented one of the early steps in the sequence of events which led to leptomeningitis. Bacteriologic stains revealed no bacteria to be present. In a section from the right parietal area (Fig. 3) note the width of the subarachnoid space and the dense collection of exudate which contains numerous degenerated leukocytes. Under higher power (Fig. 4) very few polymorphonuclear leukocytes in this portion are observed to show any degree of preservation. There were a few mononuclear cells found in some portions of the exudate. According to Walker and Johnson¹ who have studied the

reaction to penicillin in the lumbar subarachnoid space, this reaction for some reason does not resemble the usual acute inflammatory reaction, in that it contains a relatively large percentage of lymphocytes. In none of the sections studied have we noted any great number of lymphocytes. In Figure 5 one sees organisms morphologically resembling pneumococci in the exudate over the right parietal lobe. They were difficult to find, only one being found in every six to ten oil immersion fields. The diplococci observed had the usual morphology; they were not swollen and did not appear to show any of the abnormal forms which penicillin occasionally induces *in vitro* and *in vivo*. Organisms were also found in the subarachnoid exudate over the cerebrum, cerebellum and spinal cord.

Grossly we found no evidence of ependymitis. When ventricular puncture was done, it was recorded that the fluid was thick and difficult to remove. It therefore

¹ WALKER, A. E., and JOHNSON, H. C. Principles and practice of penicillin therapy in diseases of the nervous system. *Ann. Surg.*, 122: 1125, 1945.

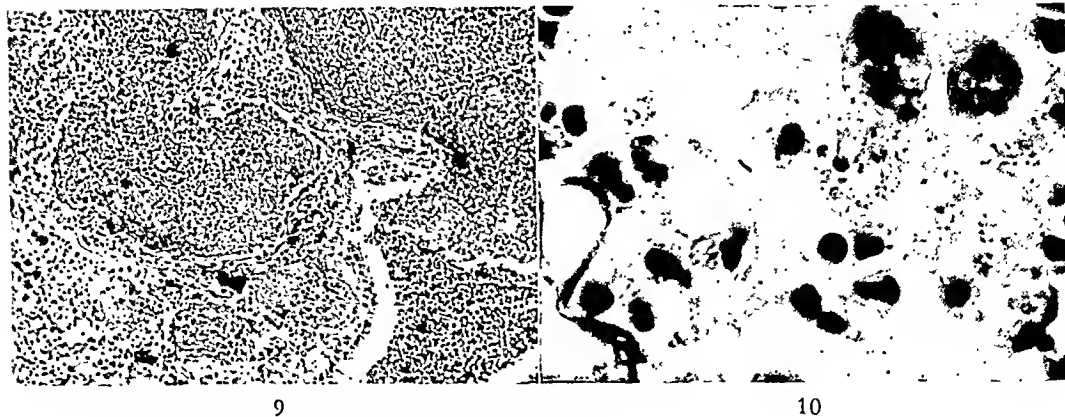


FIG. 9. A section of the lung showing early pneumonia.

FIG. 10. Section of the lung stained for bacteria. Note the presence of both cocci and bacilli.

surprised the neurosurgeons when, at autopsy, the ependyma was found to show little if any reaction. The only evidence remaining that there was any reaction in the ventricular system was found microscopically in the choroid plexus where there was a mild inflammatory reaction. (Fig. 6.) We searched the ependyma looking for a reaction in order to explain the purulent fluid reported by the neurosurgeons. The ependymal lining was normal but there were perivascular collections of cells found adjacent to the ventricles; (Fig. 7) they constitute evidence that there was an inflammatory process involving the ependyma, or at least the wall of the ventricular system. Figure 8 is a section of one of the thrombi, described by Dr. Decker, removed from the cavernous sinus. It contains platelet columns and we have no reason to doubt that it represented an antemortem thrombus, probably of very short duration, which probably appeared within the last two or three days of life; it contained no bacteria.

Figure 9 shows a section from the lung taken at the point of confluence of several bronchioles. The bronchioles and adjacent alveoli contain fibrin and well preserved polymorphonuclear leukocytes. Apparently this process again is one of recent origin. A bacterial stain (Fig. 10) showed gram-positive diplococci and bacilli staining in the manner in which gram-negative bacilli stain with the Goodpasture method. In other fields we found cocci and rods that

we identified as gram-negative. Cultures taken at autopsy from the heart's blood on media containing both para-aminobenzoic acid and penicillinase and cultured both aerobically and anaerobically for three weeks showed no growth. Material taken from the meninges was cultured and a heavy inoculum used. Dr. Beamer reported finding six colonies of *Staphylococcus aureus* and one colony of a coliform organism. He was not inclined to place significance on these findings. On culture the left lower lobe of the lung showed *Aerobacter aerogenes*, hemolytic *Staph. aureus* and alpha-hemolytic streptococci.

From what we have seen grossly and microscopically we may speculate as to the sequence of the lesions. Initially there was an otitis media. The first section showed the pachymeningitis of several days' duration. It was localized but not circumscribed. Probably the leptomeningitis followed the pachymeningitis. If we had not found the localized pachymeningitis, we could not have been too much disturbed because there are many pathways by which the infection can travel from the middle ear to the central nervous system. In this case we suspect that the pachymeningitis represented the point of entrance of the infection from the middle ear into the central nervous system. As you recall the x-ray films of the mastoid were read as negative. That finding does not rule out an area of mastoiditis which had as yet not led to destruction of air cells when it was controlled by drug

therapy. I am inclined, however, to believe that the mastoid was involved rather late, probably more recently than the dura mater, on the basis of Dr. Walsh's finding pus but no destruction of air cells; again, we do not know to what extent and for what duration the penicillin may have kept the mastoiditis circumscribed.

It is difficult to account for the purulent fluid in the ventricles. We have no evidence of ependymitis; there was some exudate on the choroid plexus and an inflammatory process within the plexus.

The dilatation of the ventricular system indicates the presence of at least a partial obstruction to the flow of cerebrospinal fluid from the ventricles into the subarachnoid space. This degree of obstruction must have been dependent upon several factors, namely, the presence of thick, purulent exudate at the lateral foramina, the increased production of cerebrospinal fluid which occurs in bacterial infections of the central nervous system and the presence of purulent exudate in the cerebral and spinal subarachnoid spaces.

Regarding the left hemiplegia and convulsions which appeared first only on the left and then became generalized, it is a common observation in children that when meningitis complicates either a mastoid or middle ear infection, convulsions or paralysis occur on the side of the ear involved. It is believed that exudate may gravitate and in the case under discussion the exudate as was described by Dr. Decker was much more prominent over the right parietal lobe. Figure 4, which showed the exudate over that lobe, was not of a magnification high enough to show the degenerative changes in the ganglion cells with satellitosis and neuronophagia. It is likely that these changes were the result of increased pressure in the subarachnoid space and the ventricular system.

Pneumococcal meningitis is notorious for the residual lesions which may persist after maximum therapeutic effect from drugs has been achieved. Such a sequence of events is particularly common in children. In a

report by Hutchins and Davies² of fifteen cases in incidence of children under two years of age treated with intrathecal as well as intramuscular penicillin there were nine recoveries and yet five of these patients showed severe enough permanent central nervous system damage that they required prolonged institutional care. Sweet and his co-workers,³ reported sixteen cases of pneumococcal meningitis with seven recoveries. Of the seven patients who recovered, two were children and both of these showed marked mental deterioration following treatment. In this case and possibly in other cases the effect on the cerebrum may be due to the pressure of subarachnoid exudate and to intraventricular pressure. Judging from the distribution of the exudate and its character, one might speculate as to whether the immediate treatment of pneumococcal meningitis should not be the introduction of penicillin directly into the cisterna rather than into the lumbar subarachnoid space. Walker and Johnson introduced 20 to 30 thousand units of penicillin into the lumbar subarachnoid space and were unable to recover any of the drug in cisternal fluid. On the other hand, when penicillin is introduced directly into the cisterna, there is good diffusion throughout the subarachnoid space and the ventricular system; indeed, the diffusion is better than when penicillin is introduced directly into the ventricles. Walker and Johnson further noted that when a normal monkey was given a large dose of penicillin intravenously, only a very minute amount appeared in the spinal fluid. If, on the other hand, sterile meningeal irritation was produced, levels of penicillin in the spinal fluid rose to between 10 and 50 per cent of the blood level. Such levels would lie in the therapeutic range and it seems fair to assume that in meningitis there is increased permeability of the blood brain barrier so that penicillin is able to reach the spinal

² HUTCHINS, G. and DAVIES, J. A. V. Penicillin treatment of pneumococcus meningitis in infants. *J. Pediat.*, 27: 505, 1945.

³ SWEET, L. K., et al. Treatment of pneumococcal meningitis with penicillin. *J. A. M. A.*, 137: 263, 1945.

fluid in significant concentration. These points are important when one is faced with treating an infection which, even if present for a short length of time, may lead to lesions that are difficult to reach with penicillin. Therefore, once the diagnosis of pneumococcal meningitis is made, particularly if the patient has been seen early in the course of the disease, it would seem that massive intravenous doses may produce satisfactory spinal fluid levels, but if this result is not achieved then direct introduction of the antibacterial agent into the cisterna or even into the ventricles seems justified.

The pneumonia which was described in this patient was probably of short duration and one might estimate from the appearance of the fibrin and leukocytes that it had been present for only two to three days. The recovery of bacteria from the lesion in the lung suggests that the organisms perhaps were penicillin-resistant since the patient had had massive doses of parenteral penicillin. If indeed they were penicillin-resistant, streptomycin may have been indicated.

In summary, we attribute the inflammatory reaction to the infectious process. We base this conclusion on the absence of lymphocytes and the presence of bacteria which show no morphologic alteration and

therefore may possibly have been viable. It is conceivable that the infectious process represented a small focus which was not reached by the antibiotic. As far as the differentiation of penicillin toxicity and infection insofar as parenchymal changes are concerned we are not able to make a definitive statement in answer to that problem. We think that the changes in the cerebrum could have been produced by the large amount of exudate and the increase in intraventricular pressure. However, it is fair to point out that in monkeys large doses of penicillin intrathecally have led to cerebral damage, convulsions and even death.

Anatomic Diagnoses: Acute seropurulent otitis media, left; focal subdural purulent pachymeningitis involving mastoid area, left; (history of acute mastoiditis, left; mastoidectomy, left, two days); acute purulent leptomeningitis involving the cerebrum, more marked on the right, base of the brain, cerebellum and spinal cord; exudate in the ventricular system; (history of antemortem isolation of pneumococcus type VII); dilatation of the lateral and third ventricles, slight; thrombus in the posterior superior third of each cavernous sinus; bronchopneumonia of the lower lobes, moderate.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Simmonds' Disease*

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SINCE Morris Simmonds first noted that marked pathologic changes in the adenohypophysis were associated with generalized cachexia, there have been numerous reports confirming this. In the review article of Escamilla and Lisser in 1942¹ a total of 101 typical clinical cases with pathologic verification were collected from the literature. Since then many other cases have been reported.³⁻²⁴

By far the most frequent cause of pituitary cachexia is post partum necrosis of the pituitary gland.^{1,2} Our first case is a typical example of such a pathologic process. Another important cause of this syndrome is a neoplastic process involving the pituitary gland. Our second case is that of a chromophobe adenoma of the pituitary gland which was surgically extirpated leading to the train of symptoms and signs of pituitary cachexia.

CASE REPORTS

CASE 1. F. T., a twenty-five year old colored female, was transferred from another hospital to the Goldwater Memorial Hospital on June 18, 1946. Her family and past history revealed that her mother had been treated for lues at the age of nineteen. At the age of twelve the patient was also treated for lues with a course of alternating hip and arm injections over a period of one year. In 1934 she had epistaxis and migratory pain, heat and swelling of nearly all her joints of about six weeks' duration. A diagnosis of rheumatic fever was made. The swelling subsided but soreness and stiffness persisted in these joints; this was aggravated by damp weather. The patient knew of no associated heart involvement.

Her illness began in June, 1943 shortly after she was delivered of a seven month stillbirth. She was admitted to the hospital with fever, dyspnea, chest pain and signs of pneumonia at the right base of the lung. Marked anemia was present. The temperature gradually fell after therapy with fluids, digitalis and blood. There was a transitory albuminuria. She was discharged after thirty-eight days with a diagnosis of lobar pneumonia, anemia and rheumatic heart disease. In October, 1943 she became pregnant for a second time and in the seventh month was again hospitalized because of a blood pressure of 200/120, albuminuria and edema of the lower extremities. On admission the patient's urine showed 1 plus albumin, 30 to 40 white blood cells per high power field and 10 to 15 red blood cells per high power field. She was also anemic. With rest and a low salt diet, her arterial pressure fell to 156/85 and the edema diminished. On May 16, 1944, five days after admission, the patient spontaneously delivered a living seven month male. The delivery was complicated by a retained placenta and copious hemorrhage. Two days post partum abdominal examination revealed tenderness in both lower quadrants. She also developed dyspnea and signs of consolidation in the lower lobe of the right lung. Hemoptysis was present and a diagnosis of pulmonary embolism was entertained. The white blood count at this time was 26,900. Penicillin was administered intramuscularly. On the fourth post partum day she had a transfusion followed by a severe reaction and a fever of 106°F. The following day a purulent discharge from the vagina was noted and her temperature was 103.6°F. The patient was treated vigorously with penicillin and fluids. The clinical diagnosis at the time was a post partum septicemia secondary to thrombophlebitis of the pelvic veins. After a very septic and stormy period she improved gradually

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and left the hospital about twenty-seven days after admission.

Following her discharge from the hospital, the patient began to complain of progressive weakness and anorexia. She lost 50 pounds of weight in three years. Her menses did not reappear and she noted a gradual loss of pubic and axillary hair. In April, 1946, about two years after her previous hospitalization, she developed a fever and because of increasing weakness and joint pains was admitted to the hospital. There she was described as an emaciated colored female. The blood pressure was 75/50. The heart was normal. The blood chemistries were essentially normal but the glucose tolerance curve was flat. She had a marked hypochromic anemia. During her hospital stay the fever and joint pains subsided with salicylate therapy.

On her initial physical examination at Goldwater Memorial Hospital the findings were as follows: Normal temperature, pulse and respirations; blood pressure 70/50 and weight 63½ pounds. She was small, poorly developed and cachectic. There was alopecia of the scalp and loss of axillary and pubic hair. The conjunctivae were pale. The gingival margins were spongy and friable and there was pallor of the oral mucous membranes and lips. The chest was thin and there was atrophy of the muscles of the pectoral girdle and of the breasts. A systolic blow was heard over the fourth intercostal space just to the left of the sternum, not accompanied by a thrill. The abdominal viscera were not palpable. Atrophy of all muscles of the extremities was present. There was some limitation of motion of elbow and finger joints. On pelvic examination the cervix felt small and atrophic and was adherent along the left vaginal wall. The vagina was very shallow. Speculum examination showed an infantile cervix.

The hemoglobin content of the blood was 8 Gm. per cent, the red blood count 3,100,000, the white blood count 6,900 with 72 per cent neutrophile polymorphonuclear leukocytes, 19 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophile leukocytes. The corrected sedimentation rate was 41 mm./hr., with a hematocrit of 23 per cent. The Wassermann and Kline tests were negative. Kidney function was markedly reduced as evidenced by elevated blood urea, low urea clearance, diminished phenolsulfonphthalein excretion and inability to concentrate urine. The fasting blood sugars ranged from 65 to 68 mg. per cent.

The creatinine was 0.7 mg. per cent and the uric acid 3.7 mg. per cent in the blood. The blood calcium, phosphorus and phosphatase were all normal. The total cholesterol was 160 mg. per cent with 83 mg. per cent esters. The total proteins were 7.1 Gm. per cent, the albumin 2.1 Gm. per cent and the globulin 5 Gm. per cent. The chlorides ranged from 630 to 715 mg. per cent. The bromsulfalein and cephalin flocculation tests were negative. The undiluted prothrombin time was 19.2 (normal 15) seconds and the dilute 61.3 (normal 40 to 42) seconds. Gastric analysis showed no free hydrochloric acid after histamine. A glucose tolerance curve showed an increased tolerance. Bone marrow, platelet count, red blood cell fragility and reticulocyte counts were all normal. The basal metabolic rates ranged from -21 to -36.

X-ray examination of the skull and all bones was negative. Chest x-rays showed accentuation of the left middle cardiac segment. The ECG showed a low T₁, diphasic T₂ and inverted T₃ and TCF₄.

The patient's course at Goldwater Memorial Hospital was rapidly downhill. Frequent episodes of epistaxis and bleeding from the gums were controlled with difficulty. The prolonged prothrombin time returned to normal with vitamin K therapy very slowly but shortly thereafter rose to abnormal levels again. She had many purulent skin infections which responded to penicillin. Treatment with adrenal cortical extract and later desoxycorticosterone acetate and thyroid extract did not result in improvement. About six weeks after admission a blood transfusion was followed by chills and fever. Two weeks later she developed enlargement of the submaxillary nodes and left parotitis, with a rise in temperature to 101°F. and lymphocytosis. Although penicillin controlled this acute infection, the white blood count remained elevated from 8,000 to 17,000 with a lymphocyte count of 50 to 70 per cent. The patient had another severe transfusion reaction in September, 1946. At that time an effort was made to increase her caloric intake by intravenous and tube feedings. Simultaneously, there was a recurrence of bleeding from her nose and gums. Attempts to correct an elevated prothrombin time by means of vitamin K therapy were not successful. The patient's condition became steadily worse. The severity of her anemia increased markedly despite therapy. The blood pressure fell to 66/38. Prior to her death the



FIG. 1. Case 1. Fibrosis of the anterior lobe of the pituitary gland which surrounds the posterior lobe. Only scattered cells of the former remain ($\times 25$).

blood urea nitrogen rose to 112.8 mg. per cent. She lapsed into shock and expired on October 24, 1946, about four months after admission.

Postmortem examination revealed the following: Grossly, the body was that of a poorly developed and markedly emaciated female negro. The brain weighed 915 Gm. It appeared small and pale. There were no gross abnormalities. The sella turcica was somewhat small but appeared to be within normal limits. The pituitary, however, was markedly decreased in size and the various parts of the organ could not be differentiated. It appeared more uniform than normal and fibrotic. Several small hemorrhagic areas were found on the inferior surface.

A small amount of amber fluid was found in the right pleural cavity. Both lungs showed congestion and mottled areas of infiltration. The heart was smaller than normal and weighed 275 Gm. The pericardial cavity was completely obliterated but otherwise the heart was normal. The liver weighed 760 Gm. and appeared pale and atrophic. On section it was homogeneous and pale yellow in color. Many small petechial hemorrhages were noticed throughout the parenchyma. Both kidneys were markedly reduced in size. The right kidney weighed 75 Gm. and the left 55 Gm. The capsules stripped with ease revealing a mottled brownish surface, showing many petechial hemorrhages. The pelves and ureters appeared

normal. The uterus was small in size and firm in consistency. The ovaries were small and atrophic. The thyroid was normal in size, shape and consistency. The parathyroids appeared normal. The adrenals showed beginning autolysis. The cortices, however, appeared to be of normal thickness.

Microscopic examination revealed the following: The capsule of the pituitary gland was markedly thickened due to fibrous tissue deposition. This was mostly acellular and in areas appeared to be hyalinized. The anterior lobe was markedly atrophic and fibrotic. Its exact delimitations were indefinite due to the merging of its connective tissue with that of the capsule. It was markedly shrunken in size and contained only small regions of cells. Some pseudoacinar formation was found, the cells being small with darkly-staining nuclei and faint translucent cytoplasm, apparently chromophobe cells. No definite basophilic or eosinophilic elements were noted. The fibrotic anterior lobe partly surrounded the posterior lobe. A few irregular spaces containing colloid material were seen in the region between the anterior and posterior lobes. The intermediate lobe was not clearly visualized. The posterior lobe was compressed but otherwise showed no marked abnormalities. (Fig. 1.)

The pericardium was thickened due to deposition of collagen. There was no evidence of rheumatic heart disease.

The capsule of the liver was not thickened. The sinusoids were congested and there was considerable atrophy of the central portions of the lobules. Many of the periportal spaces were widened and contained large collections of lymphocytes and histiocytes together with occasional polymorphonuclear cells. There was also an increase of fibrous tissue in these areas. The pancreas appeared normal except for patchy areas of fibrous tissue. Most of the glomeruli of the kidneys were altered. The capillary loops were decreased in number and showed marked fibrosis. The tubules varied somewhat in size and many of them contained red cells and hemoglobin casts. There was moderate lymphocytic infiltration of the interstitial tissue.

The periphery of the ovary was made up of cellular interlacing fibers. There were a few primordial follicles, some of which appeared to be undergoing degeneration. The central portion of the ovary was made up of collagenous

fibers, many fibroblasts, small thick-walled blood vessels and several corpora albicantes. The smooth muscle bundles of the uterus appeared normal throughout. There were many small and moderately-sized, thick-walled vessels, some of which showed complete occlusion. There was no normal endometrial lining noted.

The capsule of the adrenals appeared thickened, the cortex and medulla normal. The acini of the thyroid gland varied somewhat in size and shape but all appeared normal. They were filled with colloid which stained with the same degree of intensity. The acini were lined by low cuboidal cells.

The skeletal muscle generally was normal except for small areas where the muscle was replaced by hyalinized fibrous tissue. In these areas, there was a slight perivascular infiltration by round cells and fibroblasts. The follicles of the lymph nodes were large and irregular. The sinuses were dilated and showed a marked increase in reticulum cells and fibrous tissue.

Final Diagnoses: Atrophy and fibrosis of pituitary, apparently due to old infarction; chronic adhesive pericarditis; pericholangitis; perisplenitis; lymphoid hyperplasia of spleen; chronic glomerulonephritis; cortical atrophy of adrenals; fibrosis and atrophy of ovaries; atrophy of uterine endometrium; lymphoid hyperplasia of lymph nodes; hypochromic anemia; lobular pneumonia; pulmonary edema; cachexia.

CASE II. A. S., a thirty-eight year old single white man, was admitted to Goldwater Memorial Hospital on December 19, 1940, with the major complaints of visual disturbances of ten years' duration, weight loss and wasting and abdominal cramps of five years' duration.

The patient had been well until 1930 except for occasional attacks of severe headaches. He then had, for the first time, symptoms of left temporal hemianopsia. This persisted without any objective progression of visual impairment. In December, 1934 he began to have severe, constant, predominantly left frontal and occasionally nuchal headaches lasting for a month. The headaches then became milder but still were constant and were localized mostly over the left frontal region. He had been unable to have penile erections since the summer of 1934. In January, 1935 he experienced a sudden recrudescence of bouts of headaches, accompanied by vomiting. He was drowsy and gave a delayed response to questioning and was in-

continent of urine and feces. From that time on his gait became slow and unsteady.

He was admitted to a hospital with these complaints in February, 1935. On admission he weighed 130 pounds, was well developed and in no acute distress. He had slight bitemporal pallor of the optic disks and marked bilateral temporal visual field defects. A diagnosis of craniopharyngioma was made. X-rays of the skull showed erosion of the sella turcica which appeared to be twice the normal size. On March 14, 1935, a tumor 2 cm. in diameter, bulging from the sella turcica, was partially removed by suction and curettement. In April, 1935 the patient was reoperated upon and the tumor was removed, "leaving the floor of the fossa smooth and glistening." It was found to impinge on both optic nerves and the optic chiasm. The pathologic specimens measured together about 15 by 17 by 10 mm. Microscopically, they showed fibroblastic proliferation with diffuse lymphocytic infiltration and a large amount of normal pituitary tissue. After a stormy postoperative course the patient was discharged to the out-patient department. In June, 1935 he was rehospitalized for abdominal cramps and vomiting. He slept a great deal, yawned frequently, was mentally dull and had a delayed response to questioning. He had bilateral anosmia and the optic disks were white. He was weak and there was spasticity of both arms and legs. All deep tendon reflexes were diminished and the ankle reflexes absent. In August, 1935 he weighed 102 pounds, looked cachectic and had marked hypersensitivity to cold. His skin was dry and cold, and there was marked loss of subcutaneous tissue. He walked with a stoop.

In April, 1937 he was transferred to another hospital where his blood pressure was 100/68; scarce pubic and axillary hair were noted at this time. His abdomen was distended and extremely sensitive to pressure which elicited muscular and visceral cramps. He was treated with vitamin C, antuitrin, sodium chloride, desiccated thyroid gland and whole pituitary gland without results. There he developed painful swollen joints which resembled those of rheumatoid arthritis. X-rays of the bones showed marked decalcification.

In December, 1940 he was transferred to Goldwater Memorial Hospital. His appearance was sallow and simulated that of a little old woman. Pubic and axillary hair were absent.

His blood pressure was 120/80. Both pupils were round and equal but reacted poorly to light. He had horizontal nystagmus and both optic disks were pale. The left arm and leg were fixed in extension, the right leg in flexion. He had a right clawhand deformity. The joints were painful. There was a deformity of the fingers of the left hand with displacement of bones at the interphalangeal joints. The right foot showed a hoof deformity and the ankle was painful and swollen. All his muscles were atrophied. He weighed 70 pounds. A tourniquet test showed many petechiae below the occluded area. There was no change in the x-rays of the skull from that noted previously. During his various hospitalizations his red blood cell count was 3,800,000 to 3,900,000, the hemoglobin varied from 72 to 80 per cent. Among the abnormal laboratory findings were the following: the fasting blood sugar varied from 48 to 82 mg. per cent. A sugar tolerance curve was flat, the highest value being 97 mg. per cent one hour after ingestion of glucose. An insulin tolerance test was performed with 10 units of regular insulin resulting in a drop of blood sugar to 17.5 mg. per cent. The patient remained in insulin shock for twenty-four hours despite vigorous therapy; he recovered gradually. Just before death the serum sodium level was 124.7 mEq./L. and the serum chlorides 105 mEq./L. The serum calcium ranged from 9.4 mg. per cent to 12 mg. per cent and the phosphorus from 2.6 to 3.8 mg. per cent. The total cholesterol ranged from 246 to 138 mg. per cent with variations in the ester contents of from a trace to 200 mg. per cent. The basal metabolic rate varied between -16 and -28. The blood Wassermann reaction was negative.

During the patient's stay at Goldwater Memorial Hospital he had several severe infections of the skin of his feet and several bouts of vomiting, at one time bringing up guaiac-positive material. He also had an acute parotitis. Otherwise, his general condition remained stationary. He was well oriented, able to speak slowly and to read with moderate difficulty. He had frequent episodes of abdominal cramps. His blood pressure levels fell to 86/60 during the last year before death. In April, 1947 he was transferred to another hospital for endocrine therapy. Two weeks after admission there he suddenly went into pulmonary edema and expired.

Postmortem examination revealed the follow-

ing: Grossly, the body was that of an old wizened man, weighing approximately 55 pounds and measuring 4 feet 3 inches in height. There were marked deformities of the extremities. All muscles showed advanced atrophy. The penis was infantile and only the right testicle was found in the scrotum.

The cerebral hemispheres were approximately symmetrical. The gyri were flattened and the sulci narrowed throughout. There was a large lobulated, encapsulated tumor mass over the ventral midline of the brain which was firm, rubbery and gray. There were two main lobes of the neoplasm. The lower and more posterior part was the portion which lay within the sella turcica. It was enclosed in a dense opaque grayish-white membrane. There was a constriction between it and the lobe lying dorsal and anterior to it. This was the point of junction of the extra- and intrasellar portion of the tumor through an orifice in the diaphragm of the sella turcica. The intrasellar portion of the tumor measured roughly 3 cm. transversely, 2 cm. dorsoventrally and 13.4 cm. anteroposteriorly. The suprasellar portion of the tumor, which could not be separated easily from the overlying hypothalamus and leptomeninges, was the larger segment and measured roughly 3.5 cm. dorsoventrally, 23.4 cm. from side to side and 2.5 cm. anteroposteriorly. The right optic nerve had been displaced posteriorly and laterally for a considerable distance. Its posterior displacement was roughly 1.5 cm. It was reduced to two-thirds of its normal size. It was difficult to identify the left optic nerve but a flattened band of tissue to the left of the suprasellar portion of the tumor may have been this structure. The chiasm was attenuated to a narrow ribbon. Mid-sagittal section of the brain revealed intense compression of the hypothalamic region with invasion of the floor of the third ventricle. The interventricular foramina were partially occluded by the neoplasm. The aqueduct of Sylvius and fourth ventricle were of normal size. (Fig. 2.)

Both lungs seemed well aerated. From their dark red cut surface frothy pink fluid could be expressed. The heart was smaller than normal. The pericardium and myocardium seemed grossly normal. There was a gray nodular thickening of the free edges of the mitral cusps and slight shortening of the chordae tendinae. The liver was small, weighing 710 Gm. but otherwise appeared normal. The spleen weighed

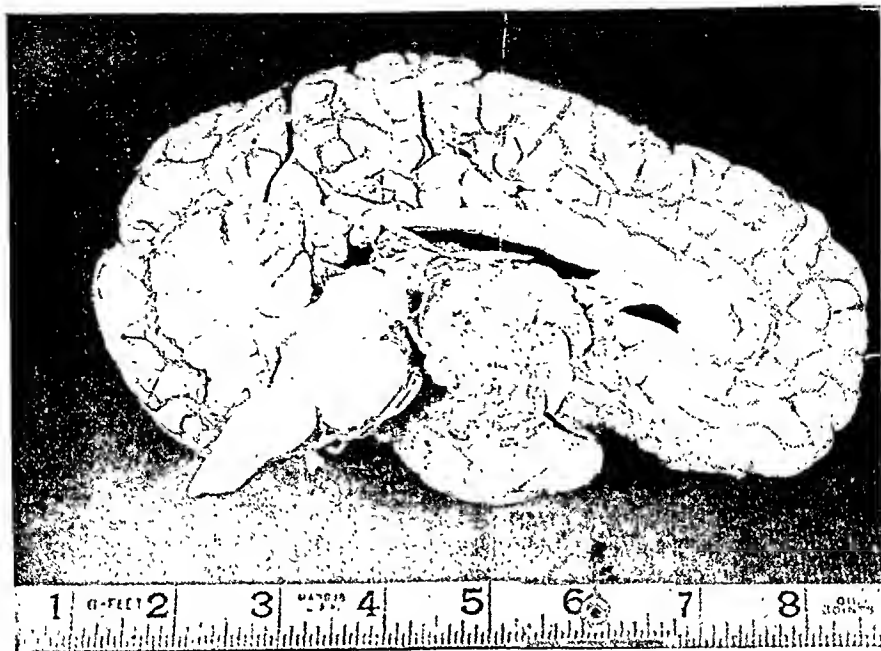


FIG. 2. Case II. Tumor of the pituitary region involving the base of the brain which has compressed the third ventricle and extended to the lateral ventricles.

45 Gm. and showed grossly a moderate increase in fibrous tissue with indistinct malpighian corpuscles. The cardiac end of the stomach showed an atrophic and thin mucosa. The small and large intestines were normal. There was a horseshoe-shaped single kidney with the open end superiorly weighing 150 Gm. The ureters arose from the lower medial portion of each side. On section the kidney appeared normal. The adrenals measured 2.5 by 2.5 by 0.2 cm. each and appeared grossly normal. The testicles were small. The thyroid gland weighed 4.6 Gm. and was rather small and firm. The parathyroids did not appear grossly abnormal.

Microscopic examination revealed the following: The intracranial tumor had a high cellular and richly vascular structure. The tumor cells were polygonal and had a moderate amount of finely granular cytoplasm. Their nuclei were uniform, oval, spherical and showed no mitosis. The cells were arranged in rows and columns about the capillaries in a regular pattern. A diagnosis of chromophobe adenoma of the pituitary gland was made. (Fig. 3.)

Sections through the heart were essentially normal except for the mitral valve which was somewhat thickened but showed no increase of cells or blood vessels. Lung sections revealed marked congestion. Some areas showed emphysema and patches of central fibrosis.

The capsule of the kidney appeared thickened. The cortex showed patches of inflammatory

cells, mostly lymphocytes. Small deposits of calcified material were seen in a few tubules. Some glomeruli were completely or partly hyalinized. The renal medulla showed a moderate amount of interstitial fibrosis. Occasional slight increase of cells in the periportal spaces of the liver were seen.

The adrenals appeared atrophic, especially the cortex which in some regions was limited to four to five rows of cells. The reticular layer appeared to be the most involved. The capsule

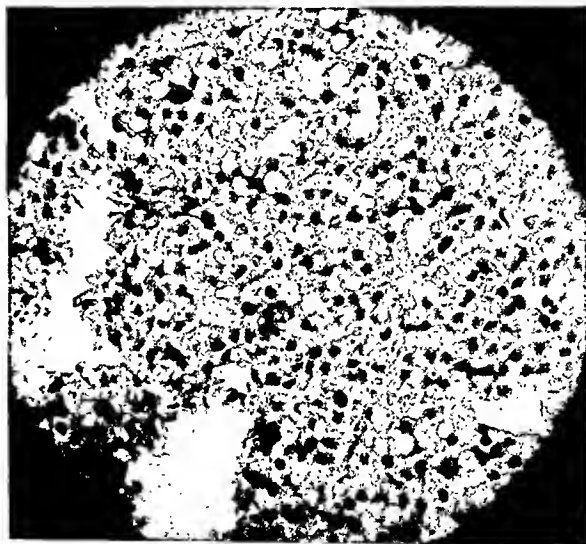


FIG. 3. Case II. Neoplastic growth of the pituitary gland consisting of cells with dark nuclei and pale cytoplasm characteristic of chromophobe cells ($\times 400$).

of the gland appeared somewhat thickened. The tubules of the testes appeared shrunken and consisted of loose fibrous structure in which few cells were found. The capsule of the thyroid gland was moderately thickened. The acini were generally small and lined by flattened cuboidal cells. Some contained colloid material which stained unevenly; others were atrophic and contained no colloid. A considerable amount of connective tissue, hyaline and calcified material was found between the alveoli. There was slight fibrosis of the parathyroid glands.

Section through bone marrow showed an increase in erythroblastic elements. The megakaryocytes were normal in number.

Final Diagnoses: Chromophobe adenoma of pituitary; emphysema and congestion of lung; horseshoe kidney; chronic arthritis; atrophy of adrenals, testes, thyroid and skeletal muscles; fibrosis of parathyroids; cachexia.

COMMENTS

The course of Case 1 is comparable with that of the cases with Simmonds' disease due to post partum necrosis as described by Sheehan.² The disease dated from the delivery which was complicated by post partum retention of the placenta, hemorrhage and puerperal sepsis. All the clinical features described by Esemilla and Lisser and by Sheehan^{1,2} were present: emaciation, absence of pubic and axillary hair, amenorrhea, loss of libido, hypotension, dry skin and atrophy of breasts and genitalia. In addition, the following laboratory findings confirmative of the diagnosis were present: low basal metabolic rate, low fasting blood sugars, high glucose tolerance, anemia and gastric anacidity.

An unusual finding toward the termination of the patient's course was the presence of lymphadenopathy with marked lymphocytosis and diminution in polymorphonuclear leukocytes in the peripheral blood. Bone marrow aspiration during life showed normal cellular elements. Dougherty and White^{26,27} have made observations which suggest that the regulation of circulating lymphocytes is under control of the anterior pituitary gland, mediated by the adrenal

gland. They also pointed out that an elevated lymphocyte count and hyperplasia of the lymphoid tissue has been recorded in Addison's disease. Selye²⁸ linked the endocrine and lymphatic systems in the so-called "alarm reaction." De la Balze and his co-workers²⁹ further suggested that there is an increase in lymphocytes and a relative decrease in neutrophils in both panhypopituitarism and Addison's disease and that the increased sensitivity to infections is due to a failure to release immune globulin from tissue. The frequent infections and the hematologic picture are in accord with the hypothesis of these investigators.

The postmortem findings were characteristic of Simmonds' disease except for the presence of a grossly and microscopically normal thyroid gland in spite of the low basal metabolic rate. In Sheehan's report about one-third of the thyroid glands studied showed normal appearance or slight atrophy only. One might conjecture that the low basal metabolic rates were a result of prolonged malnutrition.

The interest in the second case lay in the fact that the patient was a completely apituitary man since 1935 when all the contents of the sella were removed. Postmortem observation in 1947 failed to reveal the presence of any normal pituitary tissue. The patient apparently had symptoms referable to a deficiency of the anterior lobe only. Marked hypotension, visceral cramps and low blood sodium pointed to adrenal cortical insufficiency. At necropsy there was marked atrophy of the adrenal cortex.

The relationship of chronic arthritis and bizarre deformities of the extremities to his apituitarism is difficult to evaluate. We have been unable to find another case report in which this type of arthritis has complicated the course of Simmonds' disease. It has been suggested by some observers³⁰ that "hypoactivity of the pituitary may lead to increased susceptibility to infection, anemia, fatigue and generalized atrophy, conditions common in atrophic arthritis." This patient had many severe infections of the skin, parotid gland and lungs as did the first

patient. However, lymphocytosis was not found in the peripheral blood of the second patient.

SUMMARY

1. Two cases of hypopituitarism with different etiologies are described with necropsy findings.

2. The first case was typical of post partum necrosis of the pituitary and on necropsy showed atrophy of all endocrine glands with the exception of the thyroid. Lymphocytosis and lymphadenopathy were noted as a late feature. The literature on this relationship is reviewed.

3. The second case was an apituitary individual following surgical extirpation of a chromophobe adenoma. Bizarre arthritis was an unusual complicating feature.

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Friedländer Bacillus Meningitis Successfully Treated with Streptomycin*

Consideration of Friedländer Bacillus Infections in Diabetes

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THE purpose of this article is (1) to present the report of a case of Friedländer bacillus meningitis successfully treated with streptomycin† and (2) to record the significant frequency of diabetes among patients who have had Friedländer bacillus infections. The latter point, made conspicuous by our patient who had extreme hyperglycemia and glycosuria during the acute phase of her illness, has been further emphasized by a careful review of the literature relating to Friedländer bacillus infections, both of pulmonary and extrapulmonary types, in connection with the presence or absence of evidence of diabetes in the published articles.

Meningitis due to the Friedländer bacillus is a relatively rare disease and is well recognized as a highly fatal one. Prior to the sulfonamides the mortality of the disease exceeded 99 per cent, and many cases undoubtedly did not reach publication largely because they differed in no important way from those already reported. In recent years, however, chemotherapy has resulted in several cures and the syndrome has assumed new interest in medical journals.

In 1943 Ransmeier and Major¹ reported a case of Friedländer bacillus meningitis unsuccessfully treated with sulfanilamide,

† The streptomycin was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents. The Pfizer product, Lot No. 466, was used.

and in their review of the subject listed twenty-nine additional cases which had been reported up to that time. Of this group of thirty cases only three survived, one following mastoid drainage and two treated with sulfapyridine. It was estimated by Ransmeier and Major that in the large cities of the United States the Friedländer bacillus was responsible for three cases of meningitis in 3,714. In their analysis they indicated that most patients with childhood cases were seen under the age of nine months, that the years between three and twenty were surprisingly spared and that the infection appeared to show an unusual predilection for older adults and the aged.

Since the above report, three further cases of Friedländer bacillus meningitis have reached publication. In 1943 Mori² reported the infection in a twenty-six month old infant successfully treated with a sulfonamide (soluseptazine). During the same year Macky and Morris,³ reporting from New Zealand, described a fatal case of Friedländer bacillus meningitis following prostatectomy for prostatic abscess. The infection in the third case, reported by Tartakoff, Grynbaum and LeCompte⁴ in 1946, followed craniotomy for brain tumor. The patient was treated with streptomycin and although he died suddenly of pulmonary embolism, the postmortem findings were suggestive of healing meningitis and the authors believed that the antibiotic had probably been successful in controlling the infection.

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The case of Friedländer bacillus meningitis reported in this paper represents to our knowledge the first clearly defined streptomycin cure to appear and the thirty-fourth case to be reviewed in the literature.

CASE REPORT

The patient, a forty-eight year old colored female, was admitted to the Third Medical Division of Bellevue Hospital on April 11, 1946, in a comatose state. The history, which was elicited from friends and later substantiated by the patient, revealed that she had been suffering from an infection of the right middle ear for over three months, and that myringotomy had been performed at least twice with a drainage of pus. Her complaints had been few, however, until four days prior to admission when earache reappeared and was accompanied by headache. Myringotomy was again performed and the patient received three intramuscular injections of penicillin. Her complaints did not subside and two days prior to admission chemotherapy was changed to sulfadiazine, the patient receiving a total of 18 Gm. of the drug over a thirty-hour interval. Approximately twenty hours before admission the patient became feverish, thirsty and confused and she noticed an increased urinary output. After a period of irrational behavior she lapsed into coma. The past history was entirely negative except for a small amount of weight lost during the previous year. Although an aunt had diabetes, the patient had no personal knowledge of the disease in herself.

At the time of admission the temperature was 102°F., pulse rate, 136; respiratory rate, 38 and blood pressure, 145/75. The patient was a well developed and nourished comatose negress who was hyperpneic with an odor of acetone to her breath. Hirsutism of the chest and chin was present. The right ear drum was angry red and bulging, and the scar of a recent myringotomy stab was noted but without drainage. The left ear was normal and funduscopy showed no abnormalities. The remainder of the physical examination was normal except for the presence of characteristic meningitic signs with nuchal rigidity and positive Kernig and Brudzinski signs.

The blood count at this time revealed 20,000 white cells; 4,200,000 red cells and 12 Gm. hemoglobin. Spinal tap yielded a cloudy fluid

which contained 7,500 white cells, 75 per cent of which were polymorphonuclears. Of this fluid the protein measured 360 mg. per cent, sugar 286 and chlorides 660. The culture was positive for Friedländer bacilli which did not type with antisera A or B. Urinalysis showed 4 plus glucose and 3 plus acetone. The blood sugar was 445 mg. per cent.

The patient responded favorably to therapy for diabetic ketosis with infusions of 5 per cent glucose in saline and half-hourly intramuscular injections of regular insulin. Since the spinal fluid culture report was not available immediately and the smear failed to show organisms, she received combined chemotherapy with 20,000 units penicillin intrathecally at least once daily, 30,000 units intramuscularly every three hours and sulfadiazine both intravenously and by stomach tube. The dosage may be seen on the accompanying illustration. By the third hospital day the urine had cleared of acetone but showed a consistent 4 plus reaction for glucose in spite of 70 to 100 units insulin daily. Her temperature remained over 102°F., leukocytosis persisted, the spinal fluid remained purulent and the clinical condition remained critical. She was transferred to the Ear, Nose and Throat Service and modified radical mastoidectomy was performed under local anesthesia; the mastoid cortex was removed and much pus was drained from the bone, a drain being left in the wound. For the next three days, however, spinal taps continued to yield purulent fluid. On the sixth hospital day the temperature was over 103°F., white blood count was 17,500 with 75 per cent neutrophils and glycosuria continued at 4 plus in spite of administration of 150 units insulin daily, given intramuscularly at four-hour intervals with protein and carbohydrate feedings by a stomach tube. In spite of the administration of both penicillin and sulfadiazine, bacteriologic studies of samples of spinal fluid obtained on the first, fifth and sixth hospital days, and also of the mastoid drainage at the time of surgery on the third day, revealed the presence of Friedländer bacilli.

On the sixth day streptomycin therapy was instituted with 0.4 Gm. intramuscularly every four hours and 0.1 Gm. diluted in 10 cc. distilled water intrathecally once daily. Sulfadiazine was continued orally but penicillin was discontinued. Intrathecal therapy was continued for six days to a total of 0.6 Gm. and intramuscular therapy for eight days to 16.8 Gm.; the total by both

routes was 17.4 Gm. At the termination of streptomycin therapy, sulfadiazine was also discontinued; the total amount of the drug used over a twelve-day interval was 68 Gm.

During the first forty-eight hours of streptomycin therapy a marked clinical improvement

of glucose by mouth and a sustained hyperglycemia for the usual three-hour period. Spinal fluid cleared in its gross appearance and protein, sugar and chloride levels returned to normal. However, the fall in the cell count was slow. On the sixty-second hospital day, forty-nine days

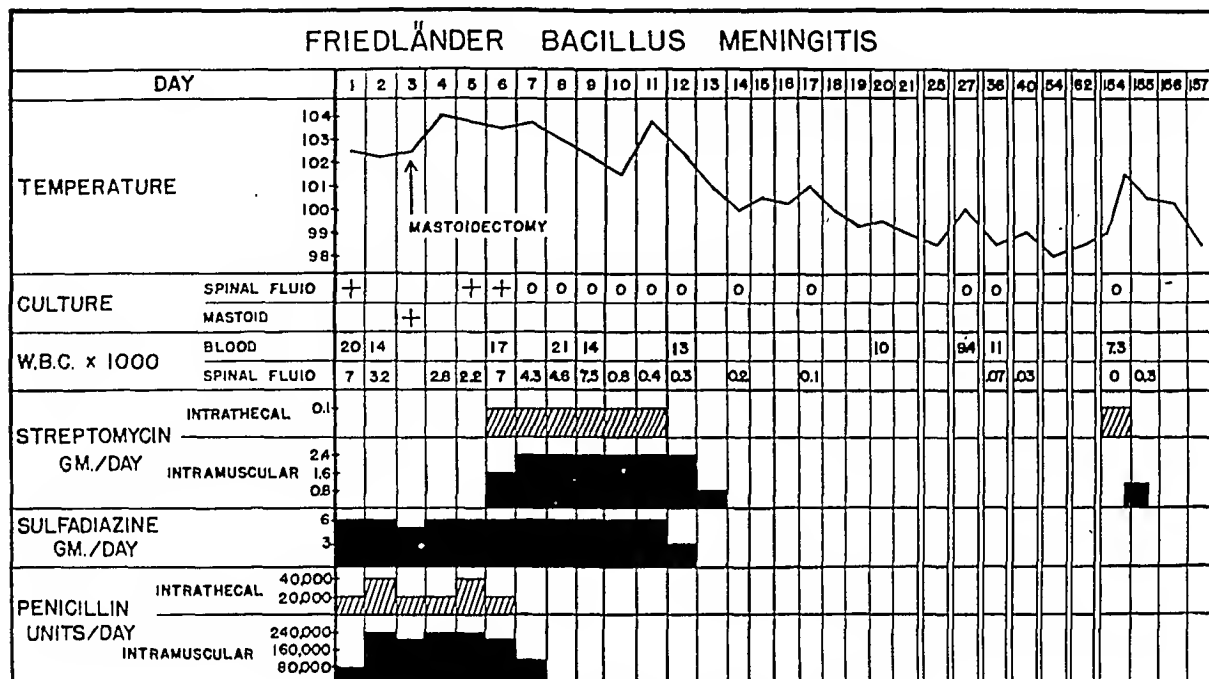


FIG. 1. Clinical and laboratory data relevant to case report.

was observed and the patient began to feed herself by mouth. By the second week the insulin requirement fell from 150 to 25 units daily, and on the twenty-fourth day she was finally regulated with 10 units protamine-zinc-insulin daily. During streptomycin therapy there was a gradual drop in temperature, but it never fell below 100°F. until the third week. On several occasions the intrathecal administration seemed to be causally followed by rises in temperature. Cultures of the spinal fluid, however, were sterile at the time of tapping twenty hours following the first intrathecal dose and remained sterile thereafter. After an early rise in the white count of the peripheral blood to 20,800 it fell to 13,000 during therapy and thereafter returned to normal levels. The temperature remained normal after the eighteenth day, and by the forty-ninth day, at which time the patient was ambulatory about the ward, the surgical mastoid wound had completely healed.

During convalescence a glucose tolerance test yielded a curve of diabetic character with a rise in blood sugar to 308 mg. per cent after 100 Gm.

after streptomycin had been discontinued, 33 lymphocytes/mm.³ were still present. At this time the patient was entirely symptom-free; physical and neurologic examinations showed no abnormality other than diminution of auditory acuity on the right and some hyperesthesia of the right forehead, orbit and cornea. She was discharged on June 12th and during the next three months she gained weight, attended the diabetes clinic and was maintained on 10 units protamine-zinc-insulin daily.

On September 18th, three months following discharge, the patient was requested to re-enter the hospital for re-evaluation and she did so although enjoying excellent health at the time. She was afebrile and the physical examination was normal. Other than for 1 to 2 plus glycosuria, urinalysis and blood count showed no abnormality. A lumbar puncture yielded a clear cerebrospinal fluid under normal pressure and containing no cells. Other laboratory findings on this fluid were: protein 66 mg. per cent, sugar 83, chloride 750. In view of the fact that her protracted fever while in the hospital sug-

gested the possibility of sensitivity to sulfadiazine or streptomycin, or both, tests were carried out. The patient was given 2 Gm. sulfadiazine orally and no reaction or temperature rise was observed. Following the spinal tap which yielded the clear, acellular fluid, 0.1 Gm. streptomycin in 10 cc. saline was again injected intrathecally, and the patient complained of poorly localized back pain for a few moments. Within the next hour, the temperature rose to 101°F., at which time she was started on a series of three intramuscular injections of streptomycin, 0.3 Gm. each, over a twelve-hour period. The temperature remained elevated at 101°F. for thirty-six hours and returned to normal only after streptomycin had been discontinued for twenty-eight hours. Before discharge the lumbar puncture was repeated and at this time the fluid was found to contain 260 white cells/mm.³, 75 per cent of which were lymphocytes. Whether or not the febrile and cytologic response represented a sensitivity reaction to or the local irritating effect of streptomycin on the meninges was not clearly established.

Comment. It appears clear that in this case, cure resulted from the use of streptomycin. Before the etiologic diagnosis of Friedländer bacillus infection was established the patient remained critically ill for six days in spite of administration of penicillin and sulfadiazine and the performance of mastoidectomy. Sterilization of the spinal fluid was achieved after the first intrathecal dose of streptomycin, and from that time rapid improvement was obvious both in the clinical picture and in the diminishing glycosuria under lower insulin dosage. The fact that the patient, in retrospect, appears to have exhibited a sensitivity to or an irritative reaction to streptomycin both with febrile response and with spinal fluid pleocytosis does not seem to have reduced the therapeutic effect of the drug in any way.

The prolonged finding of cells in the cerebrospinal fluid for six weeks following streptomycin therapy with 33 lymphocytes/mm.³ still present at the time of discharge may have been due to the drug or to the slow resolution of the extensive infection. It is interesting to note that when

the intrathecal test dose on a return visit resulted in a sterile reaction in the cerebrospinal fluid, the pleocytosis was largely lymphocytic rather than granulocytic. This finding has also been noted and commented upon by Logan and Herrell⁶ who recently reported a case of influenzal meningitis in which streptomycin therapy was followed by a persistence of lymphocytes in the spinal fluid until the time of discharge.

The value of the use of streptomycin in experimental Friedländer bacillus infections has been shown by Heilman⁶ and its use in clinical cases is now being reported. It cannot be doubted that sulfadiazine is also a valuable drug against this organism but whether or not its combination with the antibiotic is desirable remains to be determined. In this case it appeared to be ineffectual when used alone but it was continued during streptomycin therapy. Alkalinization of the urine with the use of sodium bicarbonate appears wise⁷ since both of these drugs show decreased renal toxicity with a urinary pH over 7 and streptomycin appears to be more active in an alkaline medium.⁸ It seems probable that the combination of streptomycin and sulfadiazine is the treatment of choice for Friedländer bacillus infections at the present time.

FRIEDLÄNDER BACILLUS INFECTIONS IN THE DIABETIC GROUP

In reviewing the literature on Friedländer bacillus meningitis we have been impressed by the association between this infection and diabetes mellitus. In the series tabulated by Ransmeier and Major,¹ five of the thirty cases occurred in individuals who were known to have diabetes or appeared to have had previously unsuspected diabetes prior to the occurrence of the Friedländer bacillus infection. In many of the remaining twenty-five cases the clinical information supplied is insufficient to allow decision as to whether or not diabetes existed so that this group may actually be larger than estimated. Of the three additional cases reported since that time,²⁻⁴ that of Macky and Morris³ again appears to

represent the infection in association with diabetes. Although the details supplied in this report are few and no urinary findings are included, it is mentioned that the blood sugar level a few days prior to exitus was 268 mg. per cent and that following intra-

TABLE I
CONDENSED SUMMARY OF THE LITERATURE ON ALL TYPES OF FRIEDLÄNDER BACILLUS INFECTIONS IN RELATION TO THE MENTION OF THE PRESENCE OR ABSENCE OF DIABETES

	Total	Dia-betic	Non-dia-betic	Not Stated
All cases	293	24	106	163
Pediatric cases (under 10 yr.)	25	?	?	25
Pulmonary cases	223	8	60	155
Extrapulmonary cases	45	16	21	8

venous use of 500 cc. of 20 per cent glucose and 100 units insulin, the blood sugar readings fell to 115 and 144 mg. per cent. The probability that diabetes existed in this case is suggested by the hyperglycemic figures just listed.

Because of the simultaneous occurrence of diabetes and Friedländer bacillus meningitis now reported in 7 or 20 per cent of the thirty-four cases in the literature, we have attempted to determine the incidence of this combination by a detailed examination of the published reports of Friedländer bacillus infections of all types. Unfortunately the clinical protocol of the reported case is too infrequently incomplete with respect to the presence or absence of glycosuria or hyperglycemia. Most of the papers dealing with cases of pulmonary Friedländer infection report them in summary form, omitting individual laboratory details. In spite of this, however, an inspection of the available material shows an association between diabetes and Friedländer infection which is particularly striking in the disseminated or hematogenous, non-pulmonary types of the infection while in the purely pulmonary forms of this infection, both acute and chronic, alcoholism, cirrhosis of the liver,

bronchiectasis, carcinoma, tuberculosis, arteriosclerosis, senility and debilitation appear to provide more favorable soil.

In an attempt to document the frequency of the association of diabetes and Friedländer bacillus infection as found in the

TABLE II
INCIDENCE OF DIABETES IN ALL COMPLETELY REPORTED CASES OF FRIEDLÄNDER BACILLUS INFECTIONS

	Total	No. Diabetic, Per Cent	Non-diabetic, Per Cent
All stated cases	105	24 (23)	81 (77)
Pulmonary cases	68	8 (12)	60 (88)
Extrapulmonary cases	37	16 (43)	21 (57)

literature we have reviewed and tabulated all the reported English-written cases since the first volume of the Index Medicus of 1916, with no selection of material during this thirty-year interval. All cases are included, and the occurrence of diabetes is listed as "not stated" only when clinical information is completely lacking and, although not specifically stated, the more complete protocols are considered to represent non-diabetic individuals.

Table I indicates the source material from which the more significant figures of Table II were obtained. It may be noted that in 56 per cent of the case reports the information supplied is too incomplete to allow classification with respect to the presence or absence of diabetes. It can also be seen in Table I that most of the "non-stated" cases fall into the pediatric and pulmonary forms of the disease. In Table II the "non-stated" cases of Table I have been eliminated. In this group, 23 per cent of the 105 cases of all types of Friedländer infection occurred in diabetic individuals. When the data are further analyzed, it may be noted that the incidence of diabetes among the pulmonary and extrapulmonary cases is significantly different: of sixty-eight pulmonary and thirty-seven extrapulmonary cases, 12 per cent and 43 per cent, respectively, were diabetic. These figures, par-

ticularly in the latter group, are significant enough to indicate that the association between the metabolic disorder and the bacterial infection is greater than that expected from chance.

COMMENTS

Diabetes has long been recognized as a disease predisposing to infection, most notoriously by the staphylococcus and streptococcus⁹ and the tubercle bacillus,¹⁰ and to this group the Friedländer bacillus should be added. There is no comment in the literature as to what circumstance, or set of circumstances, favors this specificity of infection.

In a search for the possible reason for this association the first and most obvious consideration suggests that the biochemical alterations seen in diabetes in some way enhance the bacteriologic growth or virulence of the selected organism or impair some factor in the defense mechanism of the patient.

The close relationship which exists between bacterial encapsulation and pathogenicity has long been recognized. The so-called soluble-specific-substance of the Friedländer bacillus capsule was studied by Goebel¹¹ and found to be a nitrogen-free, amorphous compound composed of a complex carbohydrate polymer containing hexose and hexuronic acids in varying proportions. It was shown by Avery, Heidelberger and Goebel¹² that the capsular polysaccharide of the type A Friedländer bacillus resembled that of the type III pneumococcus in some of its chemical properties, and that the type B Friedländer bacillus and the type II pneumococcus shared, in addition, an immunologic similarity.

Without the capsule, the Friedländer bacillus is an avirulent, gram-negative organism which is difficult to identify and can easily be confused with bacteria of the coli-aerogenes group. Osterman and Rettger¹³ point out that in the avirulent, acapsular phase the Friedländer, aerogenes and coli bacilli are indistinguishable, and if isolated in this form the Friedländer bacillus

would probably remain unrecognized. It has been observed by Julianelle¹⁴ and others that the R (rough) or acapsular variants are rarely encountered in human infections, and then most frequently in the chronic, low grade and less virulent disease syndromes, most of which are seen in the pulmonary form.

Julianelle¹⁴ was able to convert cultures of virulent mucoid (M), well encapsulated Friedländer bacilli into a rough (R), non-pathogenic colony by serial passage through impoverished media. However, he could not effect the transfer from R to M forms by using rapid transfers through mice, meat infusion broth or dextrose broth and concluded that the process was probably reversible but that he had not supplied the proper stimulus.

In an attempt to determine the conditions under which the Friedländer bacillus formed capsules, Hoogerheide¹⁵ in 1939 studied the influence of sugar in bacterial environment. He demonstrated that carbohydrate in the medium was not strictly necessary for capsule formation, but that capsules formed without carbohydrate were small and difficult to detect. With added sugar, however, large capsules appeared and colonies became mucoid, and he demonstrated that the glucose of the culture medium actually became a component of the capsular substance. It is significant that Hoogerheide found that at least 0.3 per cent glucose was necessary in the medium for well encapsulated bacteria to be formed, but that other sugars did not favor capsule formation as well. With smaller amounts of glucose available, encapsulation continued until all sugar had been utilized, but from that point bacterial growth and capsular formation were independent functions and could be separately stimulated by different factors.

The pH for growth of Friedländer bacilli was found to range between 5 and 9 with the optimal level at 7.5, but encapsulation appeared to be independent of pH. The optimal temperature for capsule formation was found to be 37°C., with the range extending to 42°C.

The conditions just described may be of some significance in promoting the occurrence of virulent, pathogenic Friedländer bacilli in the tissues of diabetic individuals. The minimal carbohydrate requirement in culture media of 300 mg. per cent for capsule formation is above the concentration of glucose in the body fluids and tissues of the normal individual, but may often be afforded by patients with diabetes. The optimal pH and temperature found by Hoogerheide are also at the physiologic levels, and the ranges are not exceeded by changes seen either in health or disease.

Although the cultural conditions just cited for development, *in vitro*, of encapsulation and virulence of Friedländer bacilli may play only a partial rôle if any in promoting the relatively high incidence of this infection in patients with diabetes, the occurrence of excessive sugar in each instance serves as a source of interesting speculation with regard to the apparent specificity of the bacterium-patient relationship discussed in this article.

SUMMARY

1. A case of Friedländer bacillus meningitis successfully treated with streptomycin is presented. Although sulfadiazine was used in conjunction with streptomycin, it was totally ineffective when used alone prior to the addition of streptomycin therapy.

2. In thirty-four cases of Friedländer bacillus meningitis collected from the literature, the following recoveries are recorded: (1) One before chemotherapy, a thirty-four year old male reported by Rothschild¹⁶ in 1931. Otitis media complicated by mastoiditis and subdural abscess was thought to be the primary focus, and recovery followed surgical drainage. The patient had diabetes. (2) A two year old Cuban child reported by Montes and Real¹⁷ in 1940. Cure followed administration of sulfapyridine. (3) A forty-nine year old male reported by Robertson¹⁸ in 1941. Maxillary sinusitis was thought to be the primary focus for the meningitic infection in this case, and cure again resulted after the use of sulfapyridine. This

patient also had diabetes. (4) A twenty-six month old infant reported by Mori² in 1943, with recovery following use of a sulfonamide (soluseptazine). (5) The case reported by Tartakoff, Grynbaum and LeCompte⁴ in 1946 followed craniotomy for brain tumor and was treated with streptomycin. Although the patient died suddenly of pulmonary embolization, the postmortem findings suggested that the antibiotic had probably been successful in controlling the infection. (6) The case reported in this article represents the sixth recovery among these thirty-four cases.

3. Of the thirty-four cases just mentioned the reported information is sufficiently definite to indicate that seven had diabetes.

4. In all types of Friedländer bacillus infections an analysis of the completely reported cases (Table II) indicates the occurrence of diabetes in 23 per cent of all types of Friedländer bacillus infections, in 12 per cent of pulmonary cases and in 43 per cent of extrapulmonary cases such as meningitis, liver abscess and septicemia.

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Book Reviews

The Pathology of Nutritional Disease. By Richard H. Follis, Jr., M.D. Pp. 291. Springfield, Ill., 1948. Charles C. Thomas. Price \$6.75.

This book is the first monographic presentation covering the pathologist's findings and the pathologist's point of view on the changes which occur as a result of nutritional deficiencies. As such, it is an invaluable aid to the experimental investigator in all fields which touch on nutrition. The author, now Associate Professor of Pathology at the Johns Hopkins Medical School, has had a rare background involving both experimental and observational experience in animal experimentation and the professional training of the pathologist. Dr. Follis' own publications in the field convey to the nutrition biochemist the assurance of the author's grasp of the technical phases of this special field and his interest in its aims.

To the medical man the book should be particularly welcome since it gives, in a connected account, a competent, very condensed statement of essential biochemical information and the pathologic consequences of deficiencies. Each topic ends with a statement of what is known concerning the rôle of the particular factor in human nutrition.

On the subject of deficiency states in man Dr. Follis' attitude is a critical one in the sense that he gives no space to the large mass of material published in clinical journals based on tentative evidence, casual thinking and hopeful attitudes. Dr. Follis is distinctly of the generation which includes the physiologic with the morphological changes in a consideration of pathology and it is therefore somewhat unexpected to read: "However, as one who continually observes disease at the autopsy table it is not possible—except in the case of scurvy and rickets in

infants—to be other than conservative, a leaning which perhaps has some virtue in the days of vitamin inflation." One might well ask: "Is the autopsy table the court of appeal?" even if one grants its advantages and its motives without any hesitation.

The plan of the book is simple and common sense prevails in the selection and arrangement of material. The author has struck a satisfying medium between the two functions of a book of this kind, namely, the cataloguing of material and the presentation of a line of thought, with the result that the book is decidedly readable. For some time to come this work will also be the most ready reference volume for topics in nutritional pathology. For this it is fitted with its selected bibliography of 791 references and two competent indexes.

T.F.Z.

Unipolar Lead Electrocardiography. By Emanuel Goldberger, M.D. Pp. 182. Philadelphia, 1947. Lea and Febiger. Price \$4.00.

Dr. Goldberger has written a concise, scholarly monograph on the subject of electrocardiography particularly as concerns the unipolar lead. In so doing he has contributed a great deal toward the ultimate clarification of the physiologic mechanisms involved in the science of electrocardiography. This aspect has been well handled and should prove helpful to those whose use of the electrocardiograph is more than casual. The value of the work would appear to be greatest in this respect since the author does not present a preponderance of evidence that would justify the routine use of the unipolar lead itself.

The book has been carefully assembled, the cuts are excellent and the bibliography is complete.

J.M.B

Editorial

“Intractability” in Peptic Ulcer

THE term “intractable” so frequently used in reference to peptic ulcer is difficult to define. It may refer to the patient, to the ulcer or to complications present. Ordinarily, however, it is used to indicate that the symptoms of ulcer have not been relieved by or have recurred after the use of various therapeutic procedures, usually medical, sometimes surgical. The persistence or reappearance of symptoms is accompanied as a rule by objective roentgenologic or gastroscopic demonstration of the ulcer. Two or three questions inevitably arise: Why they fail to heal? Why the recurrence? Why the refractoriness?

These questions are, of course, inseparable from the basic one of the cause of peptic ulcer and from the still older question asked by John Hunter¹ of why the stomach does not digest itself. Many details of these phenomena are still unclear, but it is evident that one of the most important factors in the protection of the normal mucosa is the layer of mucus, constantly secreted and renewed. It is also clear that the cause of peptic ulcer, long thought to be unknown, is indeed of “peptic” origin, that it results from the inability of the mucosa to withstand digestion. Very little is known regarding the mucosal factors involved in this process although Konjetzny² and Büchner³ form quite differing points of view and with

conflicting concepts have both described quite well the histologic manifestations. Wangensteen⁴ and his associates have shown that various factors, namely, posthemorrhagic anemia, shock, hemoconcentration, muscular fatigue, age, etc., abet the formation of experimental histamine ulcers in dogs. The extent to which these experiments may be translated into clinical equivalents is perhaps debatable but the principles established do seem valid. Wolf and Wolff⁵ observed that in the human stomach with increased vascularity and turgor the surface of the mucosa became more friable and susceptible to injury. This vascularity could be produced in various ways including emotional conflict and frustration. There are doubtless many factors which reduce the susceptibility of the mucosa to digestion. Some of these may explain such phenomena as the location of the lesion, the tendency to recurrence at the same point, the seasonal variation and the precipitating effect of fatigue, emotional stress and infection. However, the feasibility of controlling these mucosal factors by clinical methods seems

¹ HUNTER, J. On digestion of the stomach after death. *Phil. Tr. Roy. Soc.*, 62: 447, 1772.

² KONJETZNY, G. Die entzündliche Grundlage der Geschwürsbildung im Magen und Duodenum. Berlin, 1930. Julius Springer.

³ BÜCHNER, F. Die Pathogenese der peptischen Veränderungen. Jena, 1931. Gustav Fischer.

⁴ FRIESEN, S. R. and WANGENSTEEN, O. H. Role of hemoconcentration in production of gastric and duodenal ulcer following experimental burns. *Proc. Soc. Exper. Biol. & Med.*, 64: 81, 1947.

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⁵ WOLF, S. and WOLFF, H. G. Human Gastric Function, An Experimental Study of a Man and His Stomach. New York, 1943. Oxford University Press.

rather doubtful. Clinicians from Sippy on have, therefore, concentrated upon measures to decrease the acid-pepsin attack rather than hypothetic schemes for protecting the mucosa or increasing mucosal resistance.

Through the years there have been students of the ulcer problem who have been unwilling to accept the validity of the concept enunciated by Schwartz⁶ in 1910 of "no acid, no ulcer." Their voices have gradually been stilled as it has become established that chronic peptic ulcer occurs only in association with acid gastric juice. If a patient with peptic ulcer develops persistent achlorhydria spontaneously or after roentgen irradiation or as a result of surgery, the ulcers invariably heal and do not recur until or unless the acid gastric secretion returns.⁷ This fact has led Wangensteen⁸ to characterize the concept of "intractable ulcer" as a myth; because if sufficient stomach is removed surgically to produce permanent achlorhydria, the lesions do not recur.

This brings us back to the question of why some individuals develop peptic ulcer and others do not. Is the fault one of deficient mucosal resistance or of hypersecretion or are both factors operative? Levin's^{9,10} studies have shown clearly that with respect to duodenal ulcer there is a profound increase in the fasting or basal gastric secretion of

hydrochloric acid. While fasting, normal individuals secrete an average of approximately 680-mg. of hydrochloric acid in twelve hours whereas patients with duodenal ulcer yield an average return of 2,240 mg. In "intractable" ulcers Kirsner and Levin¹¹ have found the fasting output of hydrochloric acid to be as high as 6,353 mg. in twelve hours. This hypersecretion, as Dragstedt¹² has shown, is chiefly vagal in origin and can be profoundly reduced by complete bilateral vagotomy; subsequent healing of the ulcer occurs. In gastric ulcer the secretory situation is quite different¹⁰ for the output of hydrochloric acid is not greater than that found in normal individuals. Acid gastric juice is invariably present but not in excessive amounts; in fact, there is frequently a definite hyposecretion. It seems evident, therefore, that in gastric ulcer the primary defect is probably one of decreased mucosal resistance arising in some unknown manner: decreased secretion of mucus in a particular area, excessive friability, accidental traumatic mechanical injury of the superficial mucosal cells or some such phenomenon. In the absence of acid gastric juice such erosions heal promptly; in the presence of acid chyme the regenerative power of the mucosa is still sufficient to bring about healing in the great majority; in a relatively small number peptic digestion transforms the erosion into an ulcer which gradually increases in size and depth. The process may stop at any point for the healing tendency of the mucosa is ever present.

Sippy¹³ considered "the greatest known hindrance to the healing of the peptic ulcer . . . (to be) the disintegrating and digestive action of the gastric juice." We now know

¹¹ KIRSNER, J. B., LEVIN, E. and PALMER, W. L. Observations on the excessive nocturnal gastric secretion in patients with peptic ulcer. *Gastroenterology*, (in press).

¹² DRAGSTEDT, L. R. and OWENS, F. M., JR. Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proc. Soc. Exper. Med. & Biol.*, 53: 152, 1943.

¹³ SIPPY, B. W. Gastric and duodenal ulcer: medical cure by an efficient removal of gastric juice corrosion. *J. A. M. A.*, 64: 1625, 1915.

⁶ SCHWARTZ, K. Ueber penetrierende Magen und Jejunalgeschwüre. *Beitr. z. klin. Chir.*, 67: 96, 1910.

⁷ PALMER, W. L., RICKETTS, W. E. and HAMANN, A. The effect of achlorhydria upon the course of chronic peptic ulcer. *Tr. A. Am. Physicians*, 1948 (in press). Achlorhydria and peptic ulcer: A further study of the role of peptic activity in the pathogenesis and course of peptic ulcer. *Ann. Int. Med.*, 1948 (in press).

⁸ WANGENSTEEN, O. H. The ulcer problem. *Canad. M. A. J.*, 53: 309, 1945. Causes of failure after gastric resection for ulcer. *Wisconsin M. J.*, 44: 878, 1945.

⁹ LEVIN, E., KIRSNER, J. B., PALMER, W. L. and BUTLER, C. A comparison of the fasting nocturnal gastric secretions in patients with duodenal ulcer and in normal individuals. *Gastroenterology*, 10: 952, 1948.

¹⁰ LEVIN, E., KIRSNER, J. B., PALMER, W. L. and BUTLER, C. The fasting nocturnal gastric secretions in normal individuals and in patients with duodenal ulcer, gastric ulcer, and gastric carcinoma. *Arch. Surg.*, (in press).

that this is the attacking force responsible for the production of the lesion, the stimulus for pain and the cause of failure to heal. The digestive action of the gastric juice depends upon hydrochloric acid and pepsin; it is absent in achlorhydria. The most effective means of controlling the digestive

attack is by controlling the free acidity. We have not yet found a satisfactory method of control; therein lies the ulcer problem. Intractability would indeed be a myth if complete control could be achieved.

WALTER LINCOLN PALMER, M.D.

Lysozyme Activity in Ulcerative Alimentary Disease^{*}

1. *Lysozyme in Peptic Ulcer*

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FLYING¹ gave the name lysozyme to a bacteriolytic agent present in nasal secretions, saliva, tears and egg-white. He hoped to prove it an effective antibiotic; however, lysozyme was subsequently shown to be active against saprophytes such as sarcinae, micrococci and megatherium while most pathogens were not attacked.²

The chemical nature of egg-white lysozyme was found to be that of a basic protein of low molecular weight requiring a sulfhydryl group for its activity.³ Crystalline egg-white lysozyme was shown to have a molecular weight of about 18,000 and an isoelectric point of about 11,⁴ i.e., it is the most basic protein found thus far in warm-blooded animals. The chemical nature of other lysozymes is less well known. Recently lysozymes of acidic nature were shown in the latex of certain *Ficus* plants⁵ as well as in the latex of *Hevea brasiliensis*, in both of which the concentrations are five to twelve times that in egg-white.

Lysis of susceptible organisms by lysozyme was found to be due to the hydrolysis of a mucoid component of the cell wall.⁶ Recently this component was obtained as a high polymer mucopolysaccharide which was depolymerized and hydrolyzed at a rate comparable to the speed of bacterial lysis.⁷ The fall in the viscosity of solutions of this material made possible an accurate viscosi-

metric assay of the enzyme. One unit of lysozyme was defined as the quantity which at 37°C. and pH 5.3 reduced the viscosity of a 0.4 per cent solution of the substrate to one-half in ten minutes.

A survey of the concentrations of lysozyme in man revealed the following concentrations: (1) Tears, 800 to 2,000 u/cc.; (2) serum, 0.5 to 1.5 u/cc.; (3) saliva, 1.3 to 2.0 u/cc. and (4) cartilage, 10 to 40 u/Gm. Tear glands of laboratory and some slaughter house animals, however, showed only about 1 unit/Gm. of gland. Samples of lyophilized or acetone-dried hog gastric mucosa revealed very high titers, ranging from about 800 to 2,000 units/Gm. This fact suggested an inquiry into the physiologic and pathologic rôle of lysozyme in the alimentary tract.

An etiologic rôle for lysozyme in alimentary ulcerative disease is suggested by: (1) Distribution of lysozyme along the digestive tract. (2) Increased concentration found in alimentary ulcerative disease. (3) Removal of surface mucus by the enzyme. (4) Production of ulcerative lesions by oral administration of crystalline lysozyme.

EXPERIMENTAL

Lysozyme was assayed viscosimetrically. The substrate was prepared from *Micrococcus lysodeikticus*. Each batch of sub-

^{*} From the Departments of Ophthalmology and Surgery and the Surgical Pathology Laboratory, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y. Supported in part by the Josiah Macy, Jr. Foundation, New York, N. Y. A preliminary report of this work was published in *Proc. Soc. Exper. Biol. & Med.*, 65: 220, 1947.

strate was tested for the amount of reducing sugars liberated in two and twenty hours on incubation with crystalline egg-white lysozyme.⁷

Gastric Mucosa. Either the fresh or dried mucosa* was extracted in a porcelain mortar with quartz sand or in a tissue

samples from uninvolved areas: fundus, 18; antrum, 35; pylorus, 120; duodenum, 200.

An attempt was then made to compare more fully the lysozyme content of different areas of ulcerous and carcinomatous stomachs. Figure 1 shows the approximate areas from which the samples were obtained.

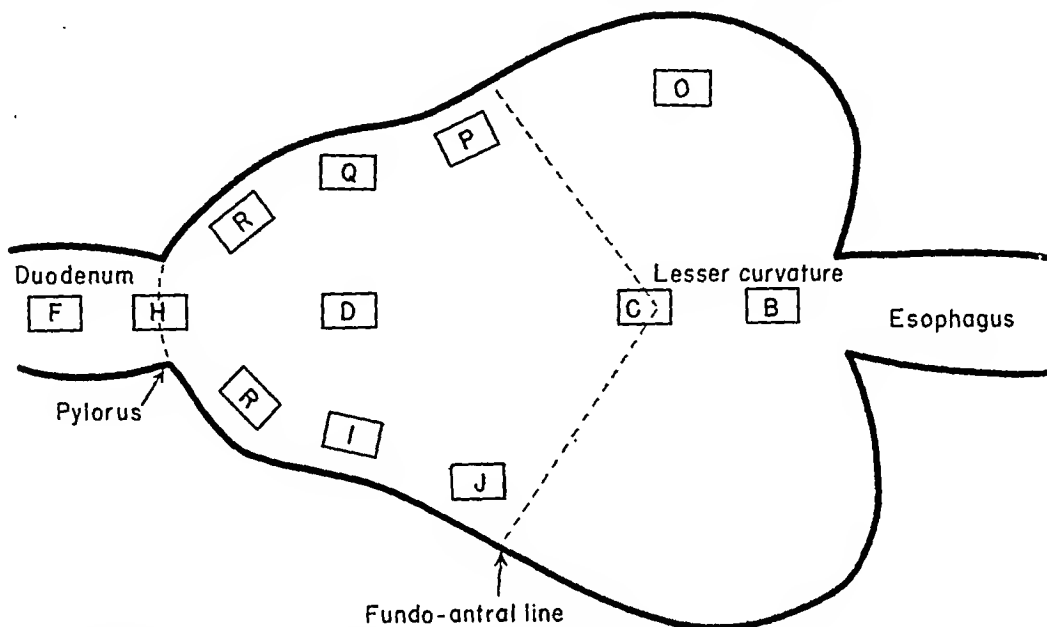


FIG. 1. Diagrammatic representation of a stomach opened along the greater curvature. The lettered blocks indicate the areas assayed.

grinder with ten times its weight of .1N HCl and centrifuged. Normal saline or buffer solutions extracted lower enzyme concentrations. For each extract the proper dilution was determined roughly and a duplicate run made in the proper dilution.

Resected human stomachs were obtained shortly after operation and samples of mucosa dissected from the submucosa. Inevitably some fibrous tissue accompanied the mucosa. The surface mucus was not disturbed by washing.

The average lysozyme concentrations of the mucosa of different histologic areas of six ulcerous stomachs and duodenums were as follows (in units per Gm. of wet weight): fundus, 16; antrum, 315; pylorus, 122; duodenum, 265. One carcinomatous stomach showed the following values in

Table I shows that the highest concentrations of lysozyme occur in the duodenum and pyloric regions where peptic ulcers occur most frequently. Any conclusions regarding the comparative values in carcinomatous and ulceratous stomachs must be highly tentative because of the small number of samples. On the basis of these results, however, there would appear to be no difference in the pyloric and duodenal regions. Factors which may have contributed to the scatter of these values are the difficulty in being certain that sections P, C and J were from the antrum rather than the fundus and the variable time elapsing between resection and assay.

Gastric Juice. Gastric juice was obtained by Levine tube aspiration, usually three hours postprandially. A few samples were procured after histamine, alcohol and Ewald meal stimulation. No significant changes in the lysozyme titers under these

* Generously prepared and furnished by the Sharp and Dohme Co. of Glenolden, Pa., and the Armour Laboratories, Chicago, Ill.

various conditions were noted even in the same individual.

Table II summarizes all data in thirty normal subjects, twenty-nine unoperated ulcer cases, six postoperative gastrectomies for ulcer patients, one chronic atrophic

TABLE I
COMPARISON OF MUCOSAL ASSAYS IN ULCEROUS
AND CARCINOMATOUS STOMACHS

Section	Ulcerous		Carcinomatous	
	Values	Mean	Values	Mean
C	2, 80, 50, 154, 13*, 13, 40, 115, 4	57.2	45	
D	388*, 526, 224, 84, 98, 185, 160*	238	121, 75, 169, 51	101
J	18, 16, 421, 50*	126	123, 428, 44	198
I	296, 140*, 204, 191	208	26, 87, 114, 67	74
Q	63, 154, 111*, 154, 130, 141, 124	125	270, 37, 55, 93	114
R	130, 298, 208, 156*	198	143	
P	41, 31*, 30, 100, 7	42	28, 37	32
F	800, 94, 272, 352, 417*, 570*, 190, 322	376	600, 362, 397, 286, 286, 299	380
H	575*, 77, 267, 157, 329, 244, 317, 101*	258	240, 260, 274	258
K	16			
B	13*, 64†	39		
O	16			

* From stomach with gastric rather than duodenal ulcer.

† From the region immediately adjacent to fundal ulcer.

gastritis patient, two gastroduodenitis cases, five vagectomized individuals before and after operation, one assay on a patient following vagectomy and gastroenterostomy and three patients with marginal ulcers.

Figure 2 shows the frequency distribution curves of the lysozyme titers of the gastric juice of the thirty normal individuals and twenty-nine unoperated ulcer patients. Both

are markedly skewed curves, but the ulcer curve has a mode of five in contrast to one of two for the normal group. In the normal series there is only one titer above 25 units/cc., whereas there are six ulcer patients with titers greater than 25. The mean titer of the normal group was 7.69 units/cc. while the ulcer group averaged 14.30. Statistical analysis of these groups revealed a possibly significant difference of the means.

Inspection of Table II reveals that all seven frankly obstructed cases (as judged by intractable vomiting) had very low lysozyme titers, ranging from 0.2 to 4.5 units/cc. with a mean of 1.77. The mean of the unoperated ulcer cases minus those with frank obstruction is 18.3 units/cc.

These low lysozyme titers in obstructed cases may be due to two factors: one, the greater dilution of the enzyme with gastric retention and two, the destruction of lysozyme by pepsin. We have no data on the dilution factor but the inactivation by pepsin was studied *in vitro*. Two types of experiments were performed: in the first experiment dried hog gastric mucosa was extracted with .1N HCl and, after centrifugation, the supernate was assayed for lysozyme before and after incubation at 37°C. A control experiment was stored for the same length of time at 4°C. and then assayed. Table III illustrates the result.

The control left for two hours at 0°C. showed exactly 714 units/Gm.

In the second experiment 50 gamma of crystalline egg-white* lysozyme was incubated with 100 gamma of crystalline pepsin containing about 50 per cent magnesium sulfate in citrate buffer of pH 2.0. The controls and incubated mixture were diluted with .9 per cent NaCl at the specified time intervals and assayed for lysozyme activity. Table IV gives the results.

In a similar experiment, substituting 100 gamma of crystalline trypsin for the pepsin

* A portion of the crystalline egg-white lysozyme was prepared in this institution. For the remainder we are indebted to the Schering Corp., Bloomfield, N. J., and to the Armour Co., Chicago, Ill. The biologic activity of these samples was identical.

TABLE II
SUMMARY OF INFORMATION ON PATIENTS HAVING GASTRIC JUICE LYSOZYME ASSAYS

Normal Subjects						
Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
W. T.	♂	35	Occasional epigastric pains; no lesion demonstrable by x-ray	104/108	Ewald	5.8
A. M.	♂	61	No complaints except for osteoarthritis	3/6	Histamine	33
H. J.	♀	42	No complaints; acne rosacea	54/58	Ewald	7.5
C. D.	♀	34	Occasional epigastric pains; no lesion demonstrable	48/54	Ewald	1.5
W. V.	♂	26	Postprandial epigastric pain; deformed duodenal bulb by x-ray; no crater	84/88	Histamine	3.6
E. C.	♂	63	Occasional epigastric pains; negative gastrointestinal series	60/64	?	1.5
T. N.	♀	41	Right upper quadrant pain; film showed diverticula of hepatic flexure; negative gastrointestinal series	54/72	Ewald	5.7
A. P.	♂	60	No complaints	30/36	Histamine	20
M. P.	♀	50	No complaints	18/22	Histamine	16.5
C. D.	♀	35	"Gas pains"; no lesion demonstrable	70/78	Ewald	2.5
J. K.	♂	29	Check-up after known ulcer; "quiescent duodenal ulcer" on gastrointestinal series	22/26	Ewald	4.8
E. W.	♀	65	"Gas on stomach"; cholelithiasis; no gastrointestinal lesion	7/28	Histamine	16.1
J. P.	♂	27	No complaints	100/108	Histamine 3 hr. post-prandially	1.82 3.32 2.2
A. N.	♀	23	No complaints			0.4
V. L.	♂	28	No complaints			1.9
K. M.	♂	47	No complaints	50/52	3 hr. post-prandially	2
I. G.	♂	25	No complaints	128/132 48/52	Histamine 3 hr. post-prandially	0.3 2 10 9.1
J. G.	♂	29	No complaints	78/84	Histamine	1.25
J. H.	♂	43	Occasional dyspepsia	18/22	3 hr. post-prandially	20 21.4
S. S.	♀	18	No complaints	50/58	Histamine	.294
F. T.	♂	28	No complaints	78/84	Histamine	.667
D. O.	♂	26	No complaints	60/64	3 hr. post-prandially	8.7 8.7
K. H.	♂	27	No complaints	54/58	Histamine	10.3
T. B.	♂	28	No complaints	140/146	Histamine	2.8
D. L.	♂	31	No complaints	0/18	Histamine	16.7
M. M.	♀	29	No complaints	120/122	Histamine	0.17
C. M.	♀	?	No gastrointestinal lesion; other complaints not known			9.1
A. M.	♂	64	No gastrointestinal complaints; peripheral neuritis; senile arteriosclerosis	84/88	Ewald	4.76
C. L.	♀	49	Gas and burning pain in left upper quadrant and over precordium for six years; greatly enlarged heart by x-ray; myocardial damage on EKG; barium enema and gastrointestinal series negative	8/32	Ewald	15.6
J. M.	♂	?	No gastrointestinal complaints	54/58	Ewald	8.8
Unoperated Ulcers						
H. J.	♂	80	Postprandial epigastric pain; antral gastritis and duodenal ulcer	86/88	Ewald	17.6
E. T.	♂	48	Bleeding duodenal ulcer diagnosed on admission; pathologic report later showed duodenal ulcer, multiple superficial gastric ulcers and lymphosarcoma of stomach	10/14	3 hr. post-prandially	40

TABLE II (Continued)

Unoperated Ulcers

Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
K. H.	♂	?	Admitted with hematemesis, melena; operation showed obstructing pyloric ulcer and multiple superficial gastric ulcers	79/87	Histamine	0.3*
J. W.	♂	30	Ulcer pain for 5 years; frequent tarry stools; vagotomy; duodenal ulcer	60/64	3 hr. post-prandially	24
A. S.	♀	71	Typical ulcer pain with prepyloric lesion; pathologic condition diagnosed carcinoma plus multiple ulcers of stomach	40/46	3 hr. post-prandially	20.7
A. L.	♀	35	Ulcer pain pattern for 2½ years; gastrointestinal series showed ulcer in duodenal bulb	38/44	3 hr. post-prandially	9.75
B. B.	♂	45	Melena and postprandial pain 4 months before admission; gastrointestinal series showed duodenal ulcer	110/120	3 hr. post-prandially	2
J. M.	♂	57	Duodenal ulcer discovered in work-up for obscure retrosternal pain	0/2	Fasting	10.4
F. G.	♂	52	Ulcer pain, hematemesis and melena; duodenal ulcer on gastrointestinal series; vagotomy	24/30	Fasting	60
J. S.	♂	63	Epigastric pain for 3 years; ulcer in duodenal bulb repeatedly demonstrated	104/112	3 hr. post-prandially	3.6
J. D.	♂	44	Vomiting for 4 months with postprandial epigastric pain for 6 months; gastrointestinal series showed duodenal ulcer	0/2	3 hr. post-prandially	7.0 } 7.5 } 5.3 average
C. D.	♂	46	6 months of epigastric pain; melena for 4 days preceding admission; gastrointestinal series showed spastic bulb and suggested a crater	86/96	3 hr. post-prandially	3.3
H. K.	♀	49	Melena and ulcer pain for 2 weeks before admission; gastrointestinal series showed spastic bulb and suggestive crater	36/40	3 hr. post-prandially	42.2
L. A.	♂	68	Ulcer pain for 4 years; duodenal ulcer seen on gastrointestinal series	83/94	3 hr. post-prandially	11.3
N. Y.	♂	?	Admitted once a year for 3 years for obstruction pyloric ulcer; gastrointestinal series showed hyperperistalsis and obstruction plus ulcer	52/60	3 hr. post-prandially	1.1*
A. S.	♂	51	Left upper quadrant pain and vomiting for 5 years; hiatus hernia and duodenal ulcer repeatedly demonstrated; had repair of hernia and vagectomy	32/38	3 hr. post-prandially	12.4
W. S.	♂	70	Gradual onset of gnawing pain 4 years before admission; bleeding on admission; has had melena, hematemesis and duodenal ulcer	78/84	3 hr. post-prandially	10.9
M. B.	♀	55	Entered for thyroidectomy (non-toxic nodular); complained of gnawing ulcer-type pain; gastrointestinal series showed duodenal bulb spasticity "consistent with ulcer"	20/24	3 hr. post-prandially	18.9
F. F.	♂	41	"Some" epigastric pain for 4 years; vomited 4 months before admission for intractable vomiting; gastrointestinal series showed pyloric ulcer plus obstruction	92/98	3 hr. post-prandially	0.4*
C. S.	♂	46	Has ulcer pain pattern and duodenal ulcer by gastrointestinal series	38/44	3 hr. post-prandially	25.4
V. M.	♂	42	Sharp epigastric pain; has had melena and hematemesis; gastrointestinal series showed ulcer on lesser curvature	10/18	3 hr. post-prandially	50.0
T. O.	♂	48	Ulcer demonstrated 7 years previously; bland diet relieved it for 7 years; ulcer pain returned in past year; had signs of perforation on admission which closed off spontaneously; had been vomiting	100/108	3 hr. post-prandially	3.8*

TABLE II (Continued)

Unoperated Ulcers						
Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
N. A.	♂	45	Epigastric pain with nausea; has hiatus hernia plus ulcer	62/74	3 hr. post-prandially	16.2
W. H.	♂	82	All complications of ulcer for over 8 years and is now vomiting	66/74	3 hr. post-prandially	0.2*
E. W.	♀	50	Characteristic ulcer pain; duodenal ulcer was repeatedly demonstrated	32/40	3 hr. post-prandially	5
F. P.	♂	61	Vague epigastric pains for 3 years and is now vomiting 6 times a day	100/109	Histamine	4.5*
H. W.	♂	51	Perforated duodenal ulcer in 1942; now vomiting and needs lavages	60/68	3 hr. post-prandially	2.1*
L. K.	♂	67	Has had a known ulcer for many years, and melena recently	120/130	3 hr. post-prandially	4.8
J. K.	♂	33	Chronic duodenal ulcer since the age of 19; now doing well on ambulatory diet; symptoms return upon indiscretion	22/26	Ewald	4.87
Marginal Ulcers						
C. L.	♂	59	Demonstrated bleeding ulcer at margin of Billroth II stoma; vagectomy	42/48	3 hr. post-prandially	62.9
D. R.	♂	55	Had Polya type gastric resection for duodenal ulcer five years ago; came in bleeding from marginal ulcer; vagectomy	0/4	3 hr. post-prandially	32.6
K. B.	♀	?	Gastroenterostomy 20 years previously; perforated marginal ulcer in November, 1946; refused vagectomy	96/98	3 hr. post-prandially	3.9
Repeat Runs on Patients Following Vagectomy						
N. A.	♂	45	Vagectomy for hematemesis and tarry stools from duodenal ulcer	0/4	3 hr. post-prandially	7.2 16.2 previous value 56% decrease
F. G.	♂	52	Classical ulcer history with melena and hematemesis; vagectomy performed	18/22	Fasting	50 60 previous value 16.7% decrease
J. W.	♂	30	Ulcer in duodenum for 5 years; gnawing pain and frequent melena; vagectomy performed	0/4	3 hr. post-prandially	10 24 previous value 58.4% decrease
D. R.	♂	55	Had Polya type gastric resection for duodenal ulcer 5 years ago; had bleeding marginal ulcer; vagectomy done	0/4	3 hr. post-prandially	27.2 32.6 previous value 16.6% decrease
C. L.	♂	59	Bleeding ulcer at margin of Billroth II stoma; vagectomy done	48/52	3 hr. post-prandially	16.2 62.9 previous value 74.4% decrease
Runs Following Gastrectomy (Hofmeister) for Duodenal Ulcer						
G. S.	♂	34	7 years of duodenal ulcer; gastrectomy; assay third postoperative day	0/28	3 hr. post-prandially	33.2
H. H.	♀	65	Multiple gastric ulcers; gastrectomy; recurrence of symptoms; no marginal ulcer seen on one gastrointestinal series	0/4	Histamine	61.6
J. L.	♀	63	Intractable ulcer pain for 30 years; gastrectomy; assay 17th postoperative day	50/56	3 hr. post-prandially	30.8
F. C.	♂	68	Intractable pain and vomiting; gastrectomy; assay 20th postoperative day	28/31	3 hr. post-prandially	46.2
C. C.	♂	63	15 years of duodenal ulcer; intractable vomiting; gastrectomy; assay 8th postoperative day	24/30	3 hr. post-prandially	15
S.	♂	?	Had burning pain following operation; exploration revealed gastric polyps	14/22	3 hr. post-prandially	22.6

TABLE II (Continued)

Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
Chronic Atrophic Gastritis Diagnosis by Gastrointestinal Series and Gastroscopy						
N. M.	♀	77	Has lost appetite with a weight loss of 40 pounds; no lesion discovered except thin gastric mucosa with shallow rugae	35/44	3 hr. post-prandially	5
Gastroduodenitis (Enlarged Rugae by Gastrointestinal Series)						
W. L.	♂	36	Mild epigastric pain at times; gastrointestinal series shows enlarged rugae	92/98	Histaminic	22 35.1 average 47.6
S. C.	♂	39	Epigastric pains of crampy nature; little relationship to food; gastrointestinal series shows gastro-duodenitis	76/80	Ewald	35.7 12.5
Assays after Gastroenterostomy for Obstruction						
J. B.	♂	66	Had pyloroduodenal ulcer with retention; gastro-enterostomy done; assay 26th postoperative day	90/96	3 hr. post-prandially	16.2
H. T.	♀	64	Intractable vomiting; marked cicatrization of pylorus seen at gastroenterostomy; assay 7th postoperative day	28/34	3 hr. post-prandially	1.9
Runs after Subdiaphragmatic Vagcctomy and Gastroenterostomy for Duodenal Ulcer						
H. J.	♂	43	Tarry stools, ulcer type pain; duodenal ulcer demonstrated; assay 9th postoperative day	36/42	3 hr. post-prandially	10.9

* Intractable vomiting.

at pH 7.0, there was no inactivation of lysozyme even after twenty-two hours. Because of this demonstrated inactivation of lysozyme by pepsin and because of the undoubted dilution of the enzyme by gastric retention, we have believed ourselves justified in omitting the seven frankly obstructed cases when comparing the mean of the ulcer group with that of the normal group. A statistical comparison of these

TABLE III

Time of Incubation in Hr.	Units of Lysozyme/Gm.	Per Cent Inactivation
0	714	0
1	445	38
2	164	77

TABLE IV

Time of Incubation in Hr.		Units per mg.	Per Cent Inactivation
4°C.	37°C.		
With Pepsin			
	0	869	0
	1	167	81
	2	74	92
	25	2.2	99.8
2		833	4.1
25		645	25.8
Without Pepsin			
	2	876	0
	25	690	20.6
25		800	7.9

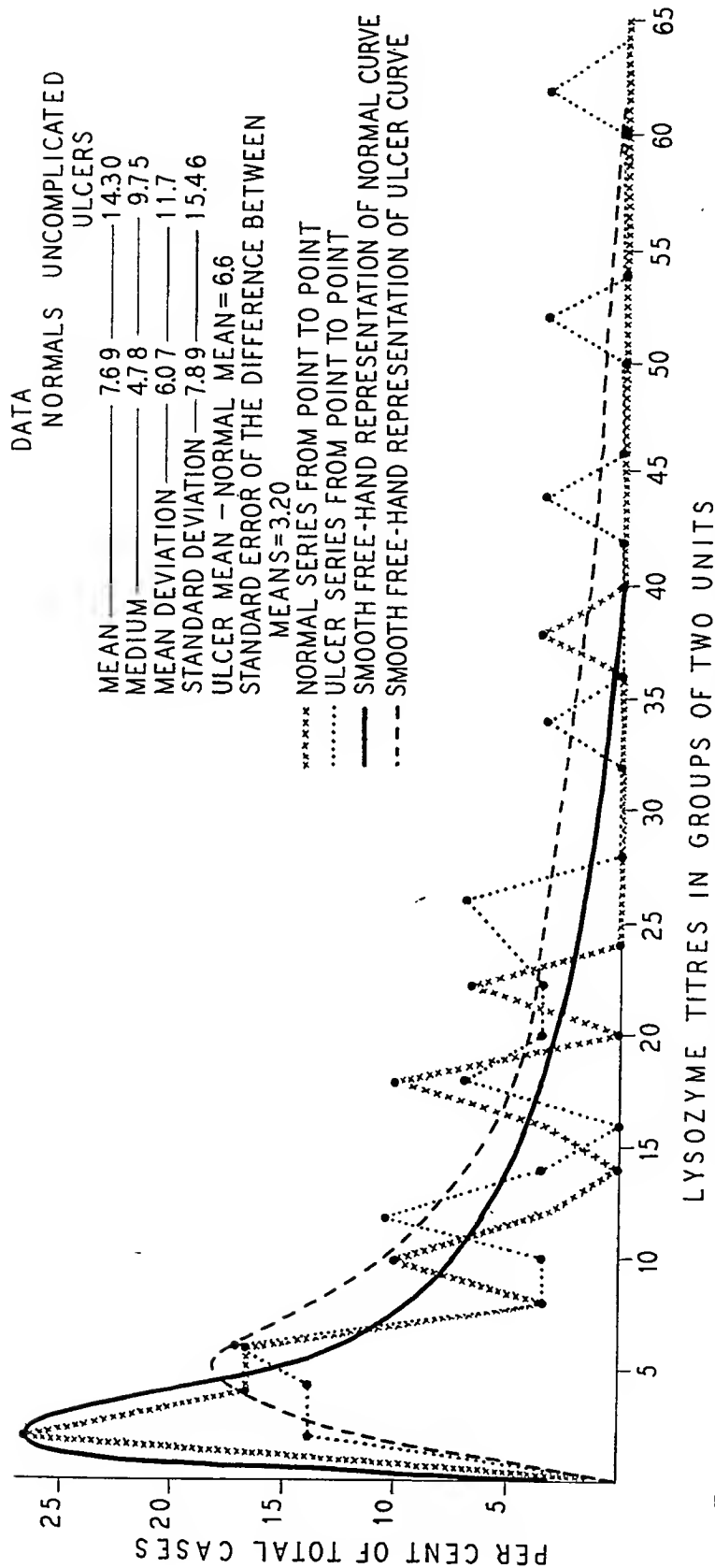


FIG. 2. Frequency distribution curves of the lysozyme titres of the gastric juice of thirty normal individuals and twenty-nine unoperated ulcer cases.

groups revealed a highly significant difference of the means.

Figure 3 illustrates various small groups of cases studied. The clinical data are summarized in Table II. The high titers in the postgastrectomy (for ulcer) cases and

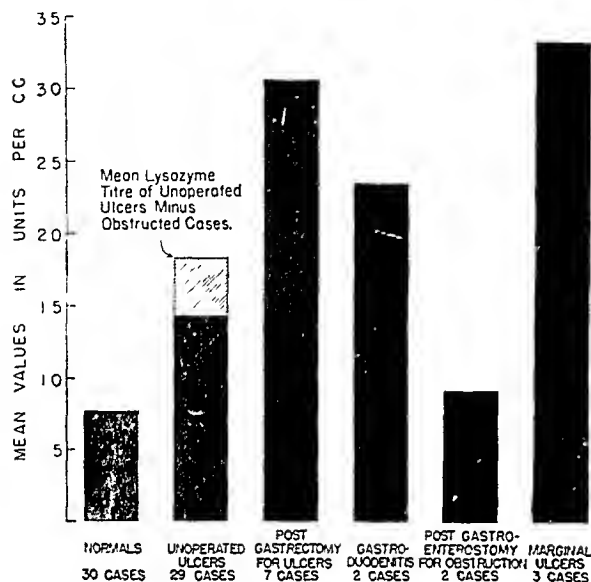


FIG. 3. Graphic representation of the mean lysozyme titers of all groups studied.

in the marginal ulcers seem significant since marginal ulcers frequently develop despite low or normal acid levels. (There was, in general, no correlation between lysozyme titers and acidity.)

Five individuals were studied before and after vagectomy. All the patients showed a decrease in lysozyme titer, ranging from 16.7 to 74.4 per cent with an average fall of 44.4 per cent. The possible connection between nervous tension and the lysozyme content of gastric juice is shown by the following observations: One individual with a negative gastrointestinal history showed on three occasions consistently elevated lysozyme titers (22, 47.6, 35.7) averaging 35.1 units/cc. The acid level was at the upper limit of normal (92/98 posthistamine). These levels were obtained while this young physician was preparing for his specialty board examinations. Because of slight epigastric pain a gastrointestinal series was done. This showed a definite antral gastritis with no evidence of ulcera-

tion. Following successful completion of the examination, the lysozyme level returned to 6.2 units/cc. with no change in the acid level. All symptoms disappeared. This single observation obviously requires further confirmation.

The gastric juices of three male patients with perforated duodenal ulcers were obtained before operation. In each case the volume was very high. The results were: (1) 2.4 units/cc., no free acid; (2) 23.1 units/cc., acidity 28/32; (3) 17.0 units/cc., acidity 40/44.

ACTION OF LYSOZYME IN THE CANINE ALIMENTARY TRACT

In order to investigate the effect of lysozyme on the mucosa of the dog the enzyme was administered to a dog with a Pavlov pouch and to dogs with intact alimentary tracts.

A Pavlov type pouch was constructed, consisting of a small amount of fundus, the antrum, the pylorus and a cuff of duodenum. It was then tacked to the skin by the duodenal cuff. After a suitable recovery period the dog was anesthetized. While supine, a solution of egg-white lysozyme in pooled human gastric juice was allowed to drip very slowly into the stoma of the pouch via a small glass intravenous needle adapter. During a four-hour period of anesthesia, lysozyme in a concentration of 7,500 units/cc. was allowed to drip from a low height into the pouch at the rate of approximately three drops per minute. All precautions possible were taken to avoid traumatizing the mucosa and to negate any possible mechanical factor in producing loss of mucus from the mucosa of the pouch. After approximately 350 cc. of this mixture had entered the pouch the latter was removed *in toto*. Following inspection, it was immediately fixed in Bouin's solution without cleansing, washing or rubbing. Gross examination of the pouch showed a remarkable "scrubbed" appearance of the mucosa. Very little mucus was to be found, an observation substantiated by microscopic examination. Representative sections were



FIG. 4. Antral mucosa from Pavlov pouch after instillation of lysozyme in pooled human gastric juice. Note cystic dilation of gastric glands.

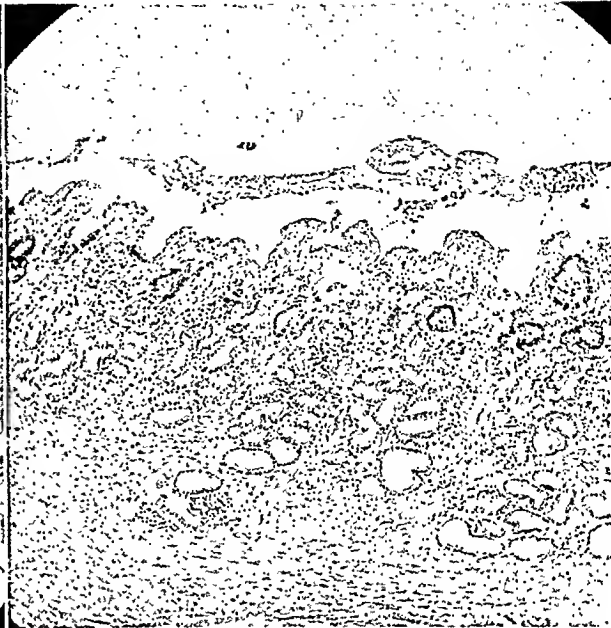


FIG. 5. Antral ulceration near pylorus from the same experiment illustrated in Figure 4.

taken of the pouch and study of the histologic preparations showed that the protective mucous coat found regularly on the mucosa of the normal stomach was completely lacking. The mucus contents of the gastric pits deep in the lamina propria disappeared, a condition which could not have been produced mechanically by a slowly flowing minute quantity of liquid on the surface of the mucosa.

Figure 4 shows complete absence of the surface mucus on the antral mucosa of the pouch used in this experiment. Also illustrated is the unusual cystic dilatation of the gastric glands deep in the lamina propria. The connective tissue of the lamina propria is edematous. It might be suspected that the cystic dilatation is due to an osmotic effect caused by the hydrolysis of a substrate in these glands.

Figure 5 illustrates a small antral ulceration near the pylorus produced in this experiment. The lesion is characterized by loss of the superficial epithelium extending well into the necks of the glands. Because of the depth of the destruction, this lesion could not have been produced by trauma.

For purposes of comparison and control the functioning stomach of the same dog

(separate from the pouch) was removed at this time and treated with exactly the same technic. Histologic examination of this gastric mucosa discloses a much greater amount of mucus on the epithelial lining of the stomach. (Fig. 6.)

In another animal experiment lysozyme was allowed to drip slowly through a Levine tube at approximately three drops per minute into a normal functioning dog's stomach (under nembutal anesthesia) over an eight-hour period. In this case the lysozyme was given in a concentration of 3,200 units/cc. of normal saline. Physiologic saline was used in this experiment in order to determine whether the dissolution of the mucus in the previous experiment was due to the gastric juice or to lysozyme activity. At the end of eight hours the stomach was resected. It was then fixed by the same careful technic without cleansing or unnecessary handling. Blocks of tissue from typical areas of this organ show much the same histologic picture. A representative photomicrograph is shown in Figure 7. The deeper mucus apparently disappears first, leaving no support for the uppermost layer which then "peels" off as shown. It would appear from comparison of the specimens

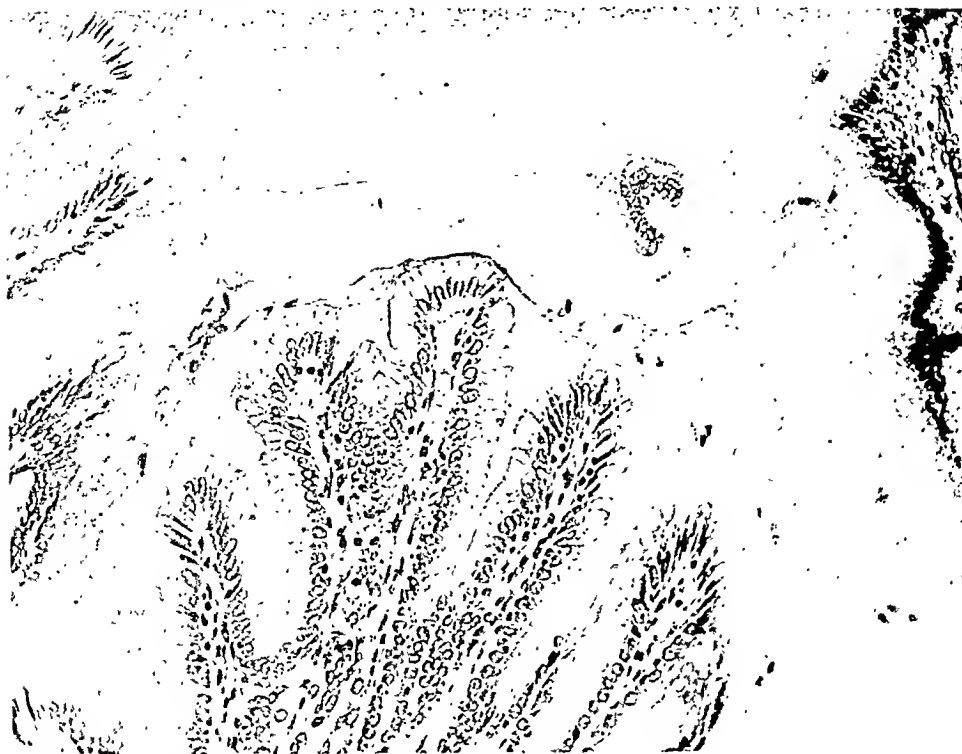


FIG. 6. Normal canine gastric mucosa from a portion of the stomach not connected with the Pavlov pouch. Note the presence of surface mucus.

from each of the two stomachs that the disappearance of the mucus is due to lysozyme.

Three normal dogs were given crystalline egg-white lysozyme by mouth. The first dog was given 30,000 units twice a day in enteric-coated gelatin capsules (approximately 42 mg. per day) for thirty-eight days, or 2,280,000 units *in toto*. The second dog received 30,000 units in 20 cc. of cherry syrup twice a day for thirty-eight days. The third received 270,000 units twice a day for three and one-half days or a total of 1,890,000 units.

The dogs showed no noticeable systemic effects from their lysozyme administrations. The second dog weighed 9.6 Kg. at the start of the experiment and 11.6 Kg. at the end. The first lost 0.3 Kg. from an initial weight of 8.5 Kg., while the third weighed 5.6 Kg. initially and 5.7 Kg. after three and one-half days. The stools were characteristically (although not always) loose, "muroid" and unformed in the dogs receiving lysozyme, while the remainder of the dogs in that animal room, receiving an identical diet, had formed stools. The

average weight of stools per day of the three dogs and one control were as follows:

	Final Weight	Average Weight Stool
Control dog.....	10.2 Kg.	38.5 Gm./day
Dog No. 1.....	8.2 Kg.	94.5 Gm./day
Dog No. 2.....	11.6 Kg.	88.5 Gm./day
Dog No. 3.....	5.7 Kg.	80.0 Gm./day

Guaiac tests on the stools of dogs Nos. 1 and 2 on three spaced occasions were consistently negative. A guaiac on the stool of Dog No. 3 was negative after two days of lysozyme administration.

Stool lysozyme assays were done on one occasion for each dog. The first dog had a level of 15.4 units per Gm. of stool (wet weight) and the second dog a titer of 6.8 units per Gm. in the midst of lysozyme administration. The third dog had a level of 91 units per Gm. on the evening of the first day of administration. These are high stool titers in comparison with the level of .04 units/Gm. obtained in the stool of one normal dog. Assuming these titers to be the



FIG. 7. Effect of lysozyme in saline on the normal canine gastric mucosa when administered by a Levine tube.

FIG. 8. Superficial ulceration in the fundus of dog (1) receiving 30,000 units of lysozyme twice a day in enteric coated capsules. Note complete absence of superficial mucosa with disappearance of the mucous cells in the necks of the glands. The parietal cells are relatively unaffected.

average lysozyme content of the stool, dogs 1, 2 and 3 put forth 1,459, 602, and 7,280 units per day, respectively.

The specimens assayed lay in the cages for a variable amount of time not exceeding two hours before they were collected. Some decrease in the lysozyme content of the stools doubtless occurred in this interval; however, a much greater part of the loss from the amount administered must have occurred within the alimentary tract.

After the stated times the dogs were autopsied and the alimentary tracts removed *in toto*. The first dog's mucosa had a hyperemic, edematous appearance throughout the small intestine whereas the stomach and colon appeared essentially normal. However, there was an apparent lack of surface mucus in the antral and pyloric areas. Five definite superficial ulcerations were noted along the small intestine. One was present in the duodenum, two in the jejunum and two in the ileum. The largest (1 by 1.2 cm.) was 5 cm. beyond the pylorus.

The second dog had essentially the same general mucosal appearance. Three ulcerations were seen, the largest in the jejunum (1 by 1.9 cm.) with two in the ileum.

The third dog showed a superficial ulcer-

ation at the pylorus; otherwise, the stomach was grossly essentially normal. The small intestine and colon were fiery red, especially the terminal ileum. Superficial serpiginous ulcerations were noted throughout the small intestine, becoming more numerous distally. The colon showed similar lesions with hyperemia and edema.

Histologically, the lesions were characterized by loss of superficial epithelium and complete lack of superficial mucus. There was fragmentation of the lamina propria, of the valvulae conniventes, with edema and extreme hyperemia of the lamina propria. In the most marked lesions extensive lymphocytic and plasma cell infiltration was noted. The microscopic findings were most marked in the terminal ileum of the third dog where there was a resemblance to regional enteritis as seen in man. Figures 8, 9 and 10 illustrate the type of lesion produced in these feeding experiments. The histologic descriptions accompany the figures.

COMMENTS

Data have been presented indicating that lysozyme activity may be an etiologic factor in the pathogenesis of peptic ulcer.

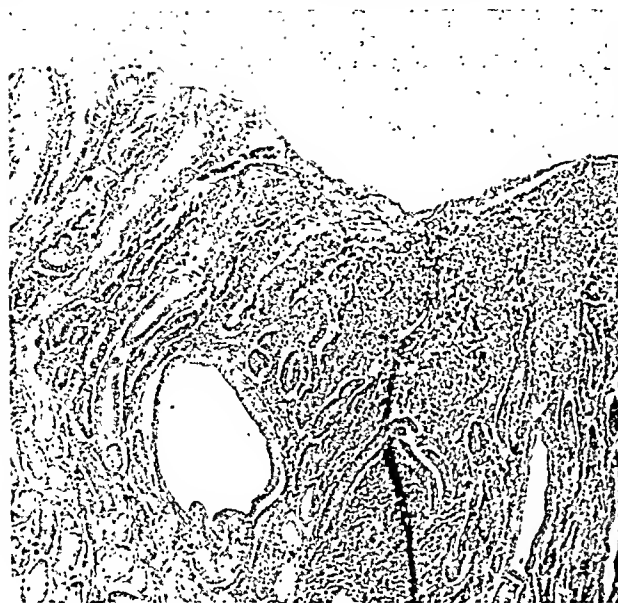


FIG. 9. Pyloric ulceration in dog (3) receiving 270,000 units of lysozyme twice a day for three and one-half days in enteric coated capsules. Note the marked cystic dilation of a gastric gland.

The distribution of lysozyme in the various histologic areas of the stomach is consistent with this supposition. One of the unanswered problems in gastric pathology has always been the fact that peptic ulcers do not ordinarily arise in the area where pepsin and HCl are produced. According to our hypothesis, the rôle of pepsin and HCl in the pathogenesis of peptic ulcer may be secondary to the removal of the surface mucus by lysozyme. The high concentration of lysozyme in the ulcer-bearing areas is in accord with this hypothesis. This supposition, like its predecessors, does not explain the occurrence of single ulcers. One would have to postulate a highly localized overproduction of lysozyme in the ulcerating area, or additional unknown factors. Lysozyme titers of the gastric juice of ulcer patients show a statistically significant but not impressive increase over those of normal subjects (compared, for example, to the increased titers of the stools of chronic ulcerative colitis). It must be assumed that the lysozyme titer of the gastric juice inadequately represents the true enzymatic activity. The volume of the gastric fluid and destruction by pepsin are factors whose influence on the lysozyme titer has not been evaluated.



FIG. 10. Deep ulceration of the terminal ileum of dog (3). The necrosis penetrates the entire thickness of the mucosa and is accompanied by an intense round cell infiltration.

The substrate of lysozyme in the human alimentary tract has not been demonstrated with certainty. The known mucopolysaccharides of hog gastric mucosa,⁸ i.e., the neutral and acid polysaccharides, are not depolymerized or hydrolyzed by lysozyme.* This was determined by viscosimetric and reductometric methods. Likewise, an enzyme mixture obtained from *Clostridium welchii*⁹ which hydrolyzed the neutral polysaccharide fraction did not contain lysozyme. This lack of information concerning the substrate is an important missing link in the argument.

The action of lysozyme on the mucosa is best illustrated by the canine experiments. Removal of the surface mucus, localized ulcerations, and intense inflammatory reactions following lysozyme administration were all produced in these studies. The relative absence of gastric disturbances in the feeding experiment as compared with the first experiments mentioned probably emphasizes the importance of the time relationship. It can be assumed that the enzyme in the deeply anesthetized dog remained in the stomach in high concentration.

* This is not surprising since in their preparation the mucosa is allowed to autolyze and is further subjected to peptic and tryptic digestion.

Egg-white lysozyme, which was employed in the canine experiments, has a pH optimum of 5.3 with an effective activity from \sim pH 3.9 to \sim pH 7.0 while human gastric lysozyme has an optimum at pH 5.93 and an effective activity range from \sim pH 4.6 to \sim pH 7.1. The shape of the pH activity curves of the two lysozymes is, however, almost identical. On purification, hog gastric lysozyme (unlike that of Ficus) behaves toward adsorption on bentonite and toward elution by various solvents exactly as does egg-white lysozyme. It might be assumed that the low pH of the gastric juice was incompatible with lysozyme activity. However, the pH of the mucus in the gastric pits and in the deeper layers of the surface mucus can be assumed to be considerably higher than that in the lumen.

In conclusion, lysozyme, like pepsin and hydrochloric acid, is a probable etiologic agent in the pathogenesis of peptic ulcer. This does not preclude the possibility of additional factors.

SUMMARY

1. Lysozyme, a mucolytic enzyme, has been found in the gastric mucosa of animals and man in a relatively high concentration.

2. The enzyme is present in normal human gastric juice.

3. In man the mucosal concentration of lysozyme is very low in the fundus and increases to a maximum in the first portion of the duodenum.

4. The mean lysozyme titer of the gastric juice of ulcer patients is increased over that of normal individuals.

5. Frankly obstructed ulcer cases showed a uniformly low lysozyme titer, due either to dilution or destruction of lysozyme by pepsin. This destruction was demonstrated *in vitro*.

6. Five ulcer subjects studied before and after vagectomy showed a mean fall in lysozyme titer of 44 per cent.

7. In one Pavloc pouch dog a superficial antral ulceration and complete removal of the surface mucus of the pouch was pro-

duced in four hours by the instillation of crystalline egg-white lysozyme in pooled human gastric juice.

8. Upon instillation of egg-white lysozyme in saline into the intact stomach of a dog for eight hours complete removal of the surface mucus without ulceration was produced.

9. In three normal dogs oral administration of lysozyme in enteric-coated capsules or in cherry syrup produced a pyloric, antral and fundal ulceration in one dog and a fundal lesion in another. All dogs showed multiple ulcerations, hyperemia and edema of the entire small intestine. In addition, one dog showed ulceration, hyperemia and edema of the colon.

10. The probable etiologic rôle of lysozyme in peptic ulcer is discussed.

Acknowledgments: We are deeply indebted to Dr. Arthur P. Stout for his encouragement and advice during this study, particularly in the interpretation of the histologic data; and we wish to acknowledge the generous support of Dr. John S. Lockwood throughout this investigation, the aid of Dr. John W. Fertig in the statistical analysis of the assay results, and the technical assistance of Miss Janice Super.

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Lysozyme Activity in Ulcerative Alimentary Disease*

II. Lysozyme Activity in Chronic Ulcerative Colitis

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A STUDY of lysozyme activity in chronic ulcerative colitis was suggested by the superficial resemblance between this disease and peptic ulcer. The presence of lysozyme in stool seems to have been established only in breast fed infants while the stools of infants fed artificially have been reported to be free of the enzyme.¹ (The tests employed were not sufficiently sensitive to detect small concentrations of the enzyme.) These findings have been confirmed by various authors² and correlated with high lysozyme titers in human milk and its absence in cow's milk. These data have been confirmed by viscosimetric measurements.³

In the present study the stools of patients with chronic ulcerative colitis were found to contain a great deal more lysozyme than those of normal individuals. Concomitant with clinical improvement the lysozyme titer falls. These facts and the experimental production of ulcerations in the small and large intestine of the dog by oral lysozyme administration, as reported in the preceding paper, suggest that lysozyme may be the chemical agent initiating the local lesions of ulcerative colitis.

EXPERIMENTAL

Stool specimens were collected† and kept frozen until ready for assay. Control experi-

† Some of these specimens from patients with chronic ulcerative colitis were obtained through the courtesy

* From the Departments of Ophthalmology, Pharmacology and Surgery and the Surgical Pathology Laboratory, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y. Supported in part by the Josiah Macy, Jr. Foundation, New York, N. Y. A preliminary report of this work was published in *Proc. Soc. Exper. Biol. & Med.*, 65: 221, 1947.

ments showed no decrease in lysozyme titer when stool specimens were kept in this manner for as long as one month. Samples of well mixed stools were weighed on an analytic balance and mixed with ten times their weight of .1N HCl. This mixture was then triturated in a mortar or tissue grinder and centrifuged. The clear supernate was then assayed viscosimetrically as described in our previous paper. When possible, a twenty-four-hour stool specimen was collected in order to determine the total twenty-four-hour output of lysozyme. The mucosal assays were handled in the same fashion as described in the preceding paper.

Table 1 summarizes the assays of individual stools for various groups of patients. This table shows a 27-fold increase in the mean titer of the chronic ulcerative colitis stools over that of the normals, and a 46-fold increase over that of the stools of normal individuals following purging. High enzyme titers were found in the surface mucus. (This material is a mixture of mucus and detritus.) In contrast to the very high titers in active C.U.C.* three stools of patients in remission (normal stool consistency, one to three bowel movements per day, absence of mucosal hyperemia and

of Dr. Henry W. Cave and Dr. Z. T. Bercowitz of the Roosevelt Hospital and the New York Post-graduate Hospital, respectively.

* Chronic ulcerative colitis is hereinafter abbreviated to C.U.C.

friability and healing ulcerations by sigmoidoscopy) showed rather low enzyme values.

Ileal stools from three patients whose C.U.C. had necessitated ileostomy had low enzyme titers, indicating that excessive

enteritis also showed a high twenty-four-hour output. The 6.7-fold increase in the daily output in the purged normals merits some comment in view of the decrease in the units of enzyme per Gm. of stool in these individuals. (Table I.) This behavior con-

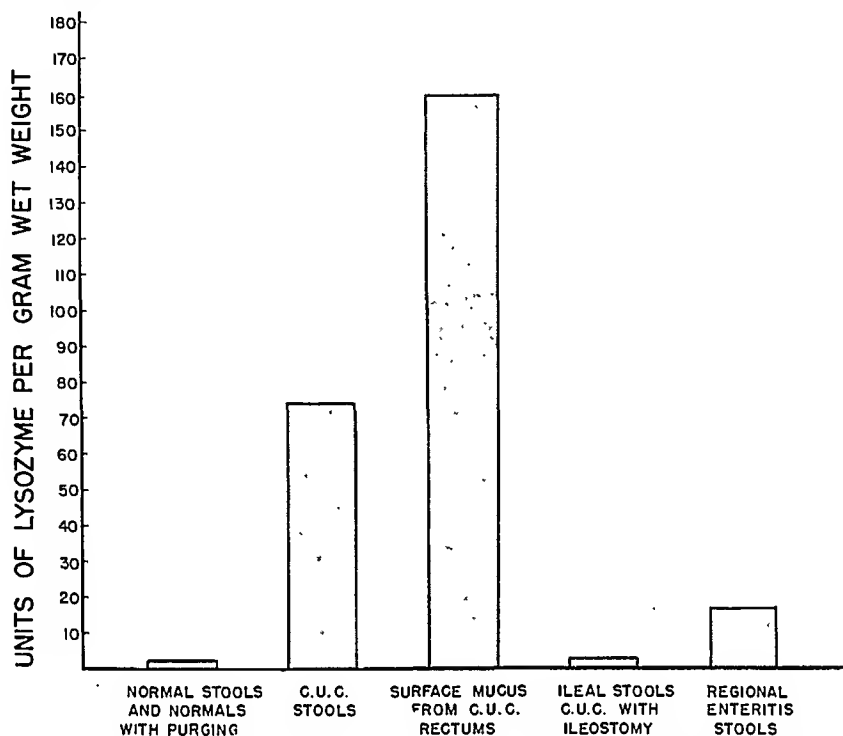


FIG. 1. A comparison of the mean lysozyme titers in four groups studied.

lysozyme is produced in the colon rather than the ileum in C.U.C. Excessive mucus in the stool apparently is not a necessary corollary of a high lysozyme titer.

Table II shows the elevated mean lysozyme titers of the stools of six individuals with regional enteritis. There is a 6-fold increase in the mean titer over that of normal stools.

Figure 1 is a graphic representation of the data in Tables I and II.

In Table III the daily output of lysozyme in various groups is tabulated. There was a 6.7-fold increase in the mean output of normal individuals with purging over that of normal stools. However, there was a 168-fold increase in the lysozyme output in stools of patients with C.U.C. over normal outputs, and a 25-fold increase in C.U.C. over the daily output in purged normal subjects. One patient with acute regional

trasts sharply with stools of C.U.C. when both the units per Gm. and the twenty-four-hour output are markedly increased. It cannot be decided at present whether the increased daily output in purging is due to an increased production of lysozyme by the mucosa or to a decreased rate of enzyme inactivation due to a rapid expulsion of the feces.

One case of acute amebic colitis and one case of non-tropical sprue showed a lysozyme content of 38 and 4.6 units per Gm. of stool, respectively. These conditions will be studied further. In a few patients with C.U.C. in whom lysozyme was assayed in the gastric juice the titers were within the normal range. Free acid was absent in two of the four patients. Tears and serum likewise showed normal lysozyme titers.

Intestinal lysozyme seems to be locally produced by the mucosa. This is suggested

by the data in Table iv. This table shows the lysozyme titers of the mucosa of various portions of the intestine. Four acute C.U.C. patients had a mean mucosal lysozyme content 8.5 times greater than that of normal colon mucosa. In quiescence pro-

TABLE I

Source	Individual Titers (Units/Gm. Wet Weight)*			Mean Titer
Normal stools (6 cases)	.5 .2	9.4 .8	4.4 .9	2.7
Normal stools (after purging with MgSO ₄ and castor oil) (8 cases)	.4 .8 1.6	3.9 1.3 3.8	1.0 .1	1.6
Chronic ulcerative colitis stools (32 cases)	28.3 49.0 33.3 24.2 35.0 49.8 84.0 86.5 109.6 78.2 21.8	48.7 10.5 47.0 119.4 25.0 125.0 20.0 18.5 22.3 40.0 502.0	22.3 180.9 103.7 4.1 46.0 125.0 160.0 9.8 87.0 39.2	73.6
Surface mucus from recto- sigmoids of chronic ulcera- tive colitis patients (6 cases)	43.5 167.0	80.0 466.0	15.7 176.5	158.1
Chronic ulcerative colitis stools, clinically in remis- sion..... (3 cases)	10.8	1.0	17.1	9.6
Ileal stools from individuals with C.U.C..... (3 cases)	.1	2.0	3.6	2.8
Stools from patients with carcinoma of rectum; much mucus..... (2 cases)	.9	2.7		1.8
Idiopathic diarrheas with much mucus..... (3 cases)	.1	1.0	5.0	2.1

* Each individual titer represents the lysozyme content of a stool specimen from a different person.

duced by surgical diversion of the fecal stream the lysozyme content of the mucosa fell to essentially normal levels. Normal ileum showed the same enzyme content as the normal colon. One patient with regional enteritis had a markedly elevated lysozyme content (33 units) in the grossly involved portion of the ileum. A specimen from the

ileum proximal to the area of gross involvement showed a slightly elevated titer. One-fourth of the ascending colon in this case was ulcerated. The lysozyme titer, however, was normal. It may be suggested that the elevated lysozyme of the ileal stool was re-

TABLE II

Source	Individual Titers (Units/Gm. of Wet Weight)			Mean Titer
Regional enteritis (6 cases)	30 12.2	7.0 42.6	.2* 6.9	16.5

* Three years postileocelectomy; persistent "watery" diarrhea, no blood or excessive mucus.

TABLE III

Source	Individual Outputs 24 Hours (Units)				Mean Out- put (Units)
Normal stools	39	528	27.5	39.5	158
Normal stools after purging	647	18.3	1940	380	1064
Chronic ulcer- ative colitis	879	582	3000		
stools	44,000	328*	64,500	4720	26,568
Regional enteritis	22,563	2080	39,200	1950	
	59,024				
	16,750				

* In "healing phase" clinically.

sponsible for this. Following ileocelectomy, this patient's stool lysozyme content fell from 30 to .5 units/Gm. The slightly elevated values found in the mucosa of the ileum proximal to regional enteritis and to retrograde involvement of the ileum by C.U.C. may emphasize the similarity of the two diseases.

Circumstantial evidence that lysozyme plays a significant rôle in the pathogenesis of C.U.C. is provided by a limited number of serial stool enzyme determinations in patients during an exacerbation of their disease and during remission. Concomitant with clinical improvement there was a fall in the lysozyme titer in the stool. In Figures 2 and 3 the results of lysozyme studies are summarized in patients who improved or failed to improve on specific therapy. These

patients received retention enemas of a 10 per cent suspension of 2-(*p*-nitrobenzene sulfonamido)thiazole (nisulfazole) in pectin.* Successful treatment of C.U.C. with this drug has been reported by Major.⁴ In our experience in the therapy of twenty-

terized by decrease in the number of daily bowel movements, disappearance of blood in the stools, improved appetite and weight gain occurring within two weeks after onset of therapy. At this time sigmoidoscopic examinations usually did not reveal im-

TABLE IV

	Type of Mucosa	Individual Lysozyme Titers				Mean Titer	Remarks
1.	Normal colon.....	4.1 3.3	3.5 3.0	3.0 10.0	8.0	5.0	Specimens from uninvolved areas of colons resected for carcinoma
2.	Biopsies from rectosigmoids of acute C.U.C. patients	42	40	54	34	42.5	All of these cases had an acute exacerbation at time of biopsy; rectal involvement proven sigmoidoscopically
3.	Mucosa from resected colons in quiescent state following ileostomy or colostomy more than 6 mo. previously	10 11 4	5 4	6 5	8 3	6.2	Although these colons were extremely fibrotic necessitating resection; there was no rectal discharge or other evidence of activity at time of resection
4.	Normal ileum.....	6.4	5.4	3.5	5.1	From ileums resected for malignancy
5.	Ileum with regional enteritis...	33.0*	This patient had ileocollectomy for regional enteritis; there were ulcers in ascending colon also
6.	Ileum proximal to regional enteritis	18.0	13*	15.5	From item No. 5 and another where side-tracking ileocolostomy was done
7.	Ulcerated colon in regional enteritis	5.4*	Specimen was from near an ulceration
8.	Ileum proximal to "retrograde involvement by C.U.C."	12	The ileum had the characteristics of regional enteritis
9.	Normal appearing ileum with entire colon involved by C.U.C.....	3.5				

* Specimens from the same patient with regional enteritis.

one patients with C.U.C. with nisulfazole there was coincident symptomatic improvement in thirteen, no improvement or a progression of symptoms in six and equivocal response in two. The patients have been followed for intervals of four to fourteen months. Improvement was charac-

pressive regression of the mucosal lesions; however, when remission was maintained there was healing of ulcerations, decrease of edema and lessened friability of the mucosa. Although three of the patients have had sustained remissions following a single course of nisulfazole (one patient is asymptomatic eleven months after therapy), in the other cases it has been necessary to

* Generously supplied by George A. Breon and Company, Kansas City, Mo.

continue small daily retention enemas of the drug in order to control symptoms. No significant toxic manifestations have been encountered. As can be seen in the figures there was a decrease in the lysozyme excretion in the patients who showed clinical

improvement. Since C.U.C. is characterized by spontaneous remissions and its course can be significantly altered by psychotherapy, we hesitate at this time to ascribe the improvement noted in our patients to nifazolin. However, the results have been

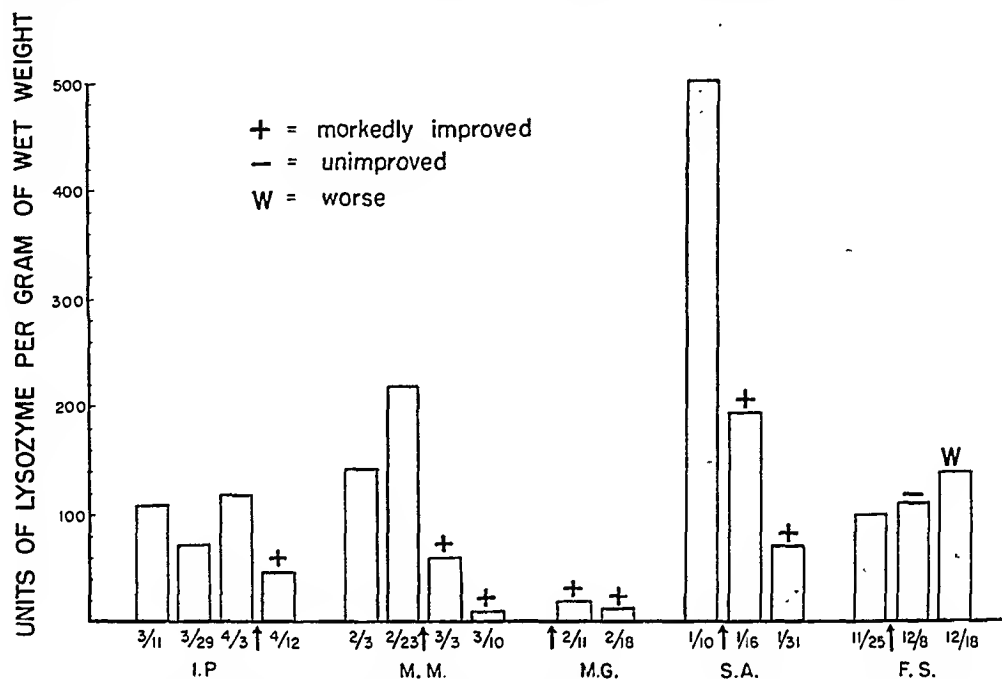


FIG. 2. The correlation between clinical status and the lysozyme content of the stool; nifazolin therapy begun in the intervals indicated by arrows.

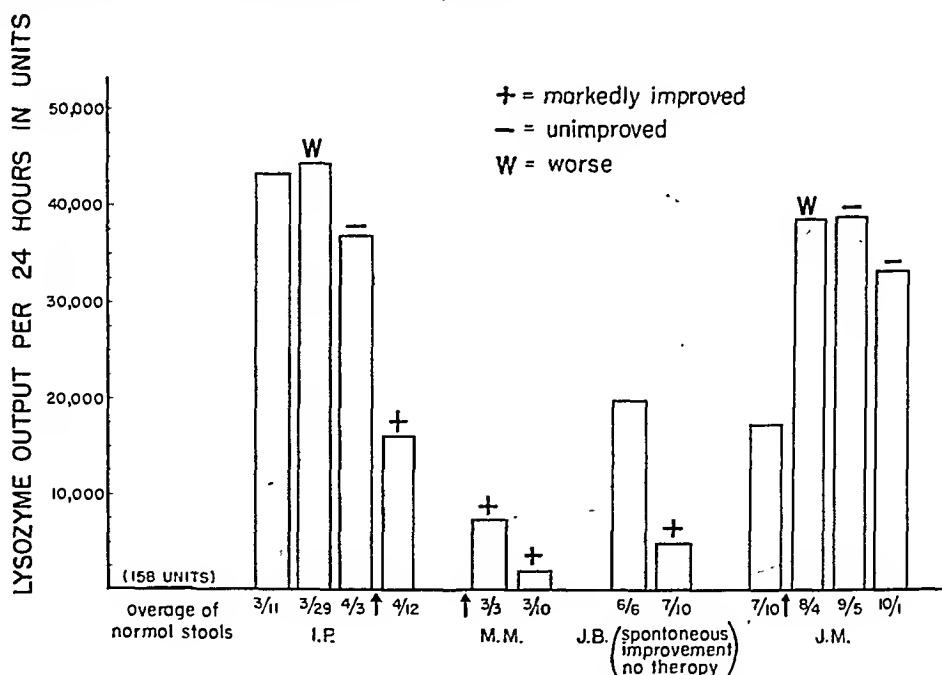


FIG. 3. Nifazolin therapy begun in the intervals indicated by arrows.

improvement whereas the titer remained high when the patients' condition was not

sufficiently encouraging to warrant further clinical trial.

The apparent efficacy of nisulfazole in the treatment of some cases of C.U.C. prompted an investigation into a possible inhibitory effect of this drug on lysozyme activity. Nisulfazole, as well as other compounds, inhibited lysozyme *in vitro* to varying degrees. This inhibition varied to a considerable extent with the source of the lysozyme and with the purity of the substrate.

Crystalline egg-white lysozyme in a concentration of 2 gamma/cc. was mixed with an equal volume of the inhibitor dissolved in saline. One cc. of the mixture was then added to 5 cc. of the substrate and the lysozyme assayed. The same dilution of lysozyme in saline served as a control.

Nisulfazole could only be tested in a concentration of 20 mg. per cent (.0007 M), its limit of solubility. The following inhibitions (in per cent) were found with nisulfazole and with equimolar concentrations of some related compounds: (1) Sulfathiazole, 25 per cent; (2) NH_4 -*p*-nitro-benzene-sulfonate, 15 per cent and (3) Nisulfazole, 42 per cent.

The multiplicity of factors involved in enzyme inhibition experiments renders interpretation difficult and at present the mechanism of this inhibition is unknown.

Use of anionic detergents as inhibitory agents was suggested by the basic nature of egg-white and mammalian lysozyme. A detailed report on these compounds will be published later. The most effective inhibitors were the normal alkyl sulfates of the series C_{10} to C_{18} .^{*} The maximum inhibition seems to be reached with the C_{16} compound. For example, in the same experiment just tabulated, Na dodecyl sulfate gave 64 per cent inhibition while hexadecyl and octadecyl sulfate in .0001 M concentration showed 85 per cent inhibition.

The lysozyme activity of human gastric juice, of extracts of human and hog gastric mucosa, of human tears and of normal human stools were inhibited to a similar degree by the alkyl sulfates. Extracts of

^{*} We thank E. I. duPont Co. for the generous gift of these compounds.

C.U.C. stools, however, were not inactivated by nisulfazole or alkyl sulfates at these concentrations. They were inhibited when the concentration of alkyl sulfates was increased 10-fold.

The reason for this discrepancy seems to be the presence of proteins in the C.U.C. stools which compete with lysozyme for the inhibitors. Thus, a 1:20 dilution of serum completely prevented the inactivation of egg-white lysozyme by .0001 M hexadecyl sulfate. The source of this increase in protein can be considered to be the serous exudate from the colonic ulcers.

COMMENT

The postulated etiologic rôle of infection in the pathogenesis of C.U.C. has fallen into disrepute because of repeated failures to demonstrate a characteristic bacterial flora in the disease. The almost uniformly high lysozyme content of the stools and mucosa, the fall in the enzyme titers with clinical improvement and the experimental production of ulcerations by administration of lysozyme to dogs all point strongly to lysozyme as an etiologic agent in chronic ulcerative colitis.

As in peptic ulcer we assume two stages in the pathogenesis of this disease: First, removal of the surface mucus with dissolution of the mucous cells and second, necrosis of the denuded tissue by proteolytic enzymes, presumably furnished by microorganisms. Similar findings in a limited number of cases of regional enteritis suggest that this also is a high lysozyme disease. The reason for localized overproduction of the enzyme in these diseases is obscure.

SUMMARY

1. The stools of C.U.C. patients have a mean lysozyme content 27 times that of normal stools.
2. The mean twenty-four-hour output of lysozyme in C.U.C. stools is 168 times that of normal stools.
3. Upon purging the twenty-four-hour output of lysozyme in normal individuals is

6.7 times that of normal stools while the concentration of the enzyme decreases by about one-third.

4. The lysozyme content of regional enteritis stools is 6.1 times that of normals.

5. With clinical improvement, the lysozyme titers and daily outputs fall.

6. The colonic mucosa of individuals with acute C.U.C. shows an 8.5-fold increase in lysozyme content over that of normal colons.

7. These data, together with the experimental production by lysozyme of ulcera-

tions in the canine alimentary tract, indicate that lysozyme is an etiologic agent which locally initiates the lesions of chronic ulcerative colitis.

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Bleeding Peptic Ulcer*

A Review of Fifty-seven Consecutive Cases

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THIS paper is a presentation of fifty-seven consecutive cases of bleeding from the upper gastrointestinal tract. This series was not chosen haphazardly but includes all cases of initial or repeated hemorrhage from peptic ulceration which came

latter age distribution lie in the fact that arteriosclerosis is present in the older patient and second, there is a prolonged duration of the disease with marked callus formation in the ulcer. Both conditions predispose to hemorrhage since they inter-

TABLE I

FINAL DIAGNOSIS OF THE UPPER GASTROINTESTINAL TRACT LESION

Lesion	Male Patients	Female Patients
Gastric ulcer.....	13	5
Duodenal ulcer.....	28	10
Gastric and duodenal ulcers combined.....	1	

under our supervision. The diagnosis in each case was compatible with either gastric or duodenal ulcer as shown by x-ray and/or by the clinical, physical and laboratory findings. There were no deaths in our series.

There were thirty-nine duodenal ulcers and nineteen gastric ulcers in our series, giving a ratio of 2.05 to 1. Duodenal ulcer is classically stated to occur from three to ten times more frequently than gastric ulcer. Thus it is seen that the location of the ulcer is not a factor in the occurrence of hemorrhage therefrom. The incidence of hemorrhage from peptic ulcer is stated to be between 10 and 30 per cent. Collins and Knowlton¹ have reported an incidence of 3.8 per cent in 2,620 cases of ulcer seen at the Cleveland Clinic.

Bleeding may take place at any age, but the majority of cases are stated to occur in the fourth and fifth decades of life. Tidmarsh² believes that the reasons for this

TABLE II

HEMORRHAGE IN FEMALES IN OUR SERIES ACCORDING TO AGE DISTRIBUTION

Ages	First Hemorrhage		Second Hemorrhage	
	No. Patients	Per Cent	No. Patients	Per Cent
20-24	2	13.33	0
25-29	2	13.33	0
30-34	0	1	14.28
35-39	0	0
40-44	2	13.33	1	14.28
45-49	2	13.33	3	42.85
50-54	1	6.66	1	14.28
55-59	2	13.33	0
60-64	1	6.66	1	14.28
65-69	1	6.66	0
70-74	2	13.33	0
Total	15	7

One female patient in the age group 40-44 experienced six separate hemorrhages before coming under our treatment.

fere with the natural factors which tend to arrest bleeding. Chaikin and Tannenbaum³ have reported a series of 121 cases of bleeding peptic ulcer with the following age distribution: second decade, nineteen patients; third decade, forty-nine; fourth decade, twenty-seven; fifth decade, eighteen and sixth decade, eight. These authors believe that hemorrhage from peptic ulcer is a disease of the younger age group and quote Goldman and Crohn who also observed this.

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Many of these patients with a history of multiple hemorrhages were not seen by us during the initial episodes of bleeding. The oldest man to hemorrhage was sixty-four years of age and the youngest was twenty-one years of age. The oldest woman to bleed

TABLE III

HEMORRHAGE IN MALES IN OUR SERIES ACCORDING TO AGE DISTRIBUTION

Ages	First Hemorrhage		Second Hemorrhage	
	No. Patients	Per Cent	No. Patients	Per Cent
20-24	1	2.38	1	9.09
25-29	2	4.76	2	18.18
30-34	4	9.52	1	9.09
35-39	4	9.52	0
40-44	10	23.80	2	18.18
45-49	10	23.80	1	9.09
50-54	3	7.14	1	9.09
55-59	5	11.90	2	18.18
60-64	3	7.14	1	9.09
Total	42	11

One patient in the age group 50-54 had four separate hemorrhages before coming under our care.

was seventy-two years of age and the youngest was twenty-three years old. Our data, therefore, concur with that of Tidmarsh in that hemorrhage was more prevalent either for the first time or as a repeated episode in the age groups of the fourth decade and above. The ratio of males to females experiencing hemorrhage from peptic ulcer has been reported as 9.5 to 1.³ We also found that this condition occurred more frequently in the male than in the female, there being forty-two males to fifteen females in our series, a ratio of 2.8 to 1.

TABLE IV

BODY BUILD OF PATIENTS IN OUR SERIES

Weight	Males	Females	Combined Percentages
Average weight.....	17	5	38.59
Obese.....	11	6	29.82
Tall, slender and under-nourished.....	12	4	28.07
Not stated.....	2	0	3.5

Although peptic ulcer is classically stated to occur in the tall, lean, square-jaw, nervous individual, it may be found in individuals of any body build.

From our figures it would seem that body build was not a pertinent factor either

TABLE V

X-RAY FINDINGS OF THE UPPER GASTROINTESTINAL TRACT IN OUR PATIENTS

Lesion	Males	Females
Gastric ulcer.....	7	1
Duodenal ulcer.....	21	5
Combined duodenal and gastric ulcer	1	0
Negative x-ray findings*.....	8	1
None taken†.....	5	8

* X-rays were not taken sooner than two weeks after the bleeding began and the patient had been put on strict ulcer management. It is recognized that the superficial ulceration may have healed during this interim.

† These patients were x-rayed previously in other institutions and the results were made available to us. They were also followed clinically for a sufficient length of time to rule out malignant lesions without x-ray.

in the incidence of ulcer occurrence or predisposition to hemorrhage.

There has been considerable debate regarding the time when the patient with bleeding from the upper gastrointestinal tract should be x-rayed. Some clinicians have recommended that the patient have fluoroscopy and x-rays as soon as possible but no manipulation of the stomach or duodenum should be carried out. Other clinicians believe that the patient should be x-rayed two or three weeks after bleeding has ceased. A strong argument against the latter procedure is that the x-ray findings are frequently negative after two or three weeks since healing has taken place on the medical regimen. We have always delayed taking x-rays of our patients for at least two weeks after the bleeding has ceased for fear that undue manipulation of the abdomen might precipitate severe hemorrhage.

We also believe that fluoroscopy carried out without manipulation and x-rays taken at the time of hemorrhage frequently fail to show any gastrointestinal lesion. Any

manipulation of the patient's abdominal wall, stomach or duodenum immediately after hemorrhage is exceedingly dangerous and must be avoided. One of the most severe cases of bleeding from a proven peptic ulcer in our series started approximately ten minutes after the patient's abdomen had been palpated in the course of a routine physical examination. Alvarez⁴ has called attention to the fact that severe gastric hemorrhage may be produced by violent abdominal massage.

Rafsky and Weingarten⁵ believe that the following factors play a definite rôle in precipitating gastrointestinal hemorrhage: upper respiratory infections, alcoholic beverages, emotional disturbances, dietary indiscretions, physical exertion and overwork.

Any bleeding from an ulcer denotes activity of the lesion. Erosion or superficial ulceration of the duodenal or gastric mucosa may cause massive hemorrhages. A penetrating ulcer of either the stomach or duodenum with penetration into the head of the pancreas frequently brings on massive bleeding. A branch of the superior pancreaticoduodenal artery is involved in such an ulcer. Ulcers occurring along the lesser curvature of the stomach also account for many cases of massive hemorrhage because of their proximity to the left gastric artery. It must be stressed that a perforating ulcer will bleed. The mechanism of this bleeding is the erosion of a vessel in an organ to which the ulcer becomes attached, with perforation at the periphery taking place simultaneously.⁷

According to Bockus,⁶ the bleeding point in hemorrhagic peptic ulcer is frequently found in the lateral wall of a blood vessel. Thrombosis within the vessel with resulting organization and obliteration of the bleeding point frequently occurs to save the patient's life. In other cases, especially in patients who present considerable arteriosclerosis, the eroded blood vessel lies in the scarred ulcer base as a stiff vessel with its lumen presenting. This does not permit retraction and constriction of the lumen so that fatal hemorrhage may occur.

Most hemorrhages from peptic ulcer do not result from penetration into a large vessel. Rivers and Wilbur⁸ have shown that hemorrhage may occur from small congested vessels which surround the ulcerated area or from vessels in the buds of vascular

TABLE VI
GASTROINTESTINAL SYMPTOMS BEFORE FIRST HEMORRHAGE
(MULTIPLE COMPLAINTS NOTED IN MOST CASES)

Symptom	No. Patients
Epigastric pain one to four hours after meals which was relieved by food and alkali.	39
Exacerbation of epigastric pain after meals in the spring.	22
Exacerbation of epigastric pain after meals in the fall.	21
"Gas on stomach".	14
Fullness in the epigastrium immediately after eating.	9
Epigastric night pain relieved by food or alkali	8
Nausea.	5
Belching.	4
Vomiting (not blood).	3
Lower mid-abdominal pain.	3
Weight loss.	3
Constipation.	2
Anorexia.	2
"Acid stomach".	1
Epigastric tenderness.	1
Epigastric pain not relieved by food.	1
No complaints mentioned.	6

granulation tissue seen in the base of an ulcer. Peptic ulcers tend to heal rapidly following severe hemorrhage. Bockus⁶ states that if pain persists following severe bleeding, there is usually continuation of the bleeding and lack of healing in the ulcer.

The duration of gastrointestinal symptoms before the first hemorrhage was variable. In our series there was an average lapse of 5.64 years in the case of males and 7.6 years in the case of females from the time of the onset of the first symptoms until the first hemorrhage took place. The longest interval between the initial symptoms and bleeding in the case of a male patient was fifteen years and the shortest duration was two weeks. In one of our female patients the longest interim period was twenty-five years and the shortest was six months. It was not possible in our series of cases to determine accurately the time interval that the patient had had adequate treatment before the first hemorrhage since many patients have

a tendency to follow an ulcer diet only long enough to obtain temporary relief and then attempt a dietary regimen of their own selection. Other patients fail to seek medical advice until gastrointestinal bleeding has actually occurred.

TABLE VII

TIME OF YEAR OF ONSET OF BLEEDING IN OUR PATIENTS
(INCLUDING MULTIPLE HEMORRHAGES)

Month	No. Patients
January.....	9
February.....	11
March.....	15
April.....	10
May.....	5
June.....	4
July.....	1
August.....	3
September.....	6
October.....	11
November.....	2
December.....	6

Rafsky and Weingarten⁵ in their series of bleeding peptic ulcers noted that the greatest number of hemorrhages occurred from the latter part of October to the latter part of March. This period of time corresponds with the increase of upper respiratory infections. Analysis of our data confirms the observations made by these authors. Eight of our patients noted onset of their hemorrhages between 7 A.M. and 12 noon; two patients noted onset of their bleeding between 12 noon and 11 P.M. and two pa-

TABLE VIII

AVERAGE TIME INTERVAL BETWEEN HEMORRHAGES

Sex	First and Second Hemorrhage		Second and Third Hemorrhage	
	Years	No. Patients	Years	No. Patients
Male.....	3.78	13	6	1
Female.....	7	7	1	1

In the case of one male patient one year elapsed between the third and fourth hemorrhages. The female patient who hemorrhaged six times had an interim of six months between the third and fourth hemorrhages, two months between the fourth and fifth episodes of bleeding and one year elapsed between the fifth and sixth hemorrhages.

tients began to bleed between 11 P.M. and 7 A.M.

A further study of our cases reveals that once a patient has had hemorrhage from a peptic ulcer there is a strong possibility

TABLE IX
SYMPTOMS AND SIGNS AT ONSET OF GASTRODUODENAL HEMORRHAGES

Symptom	No. Patients
Pallor.....	46
Tarry stools.....	39
Emesis of dark blood.....	30
Weakness.....	30
Severe epigastric pain relieved by alkali.....	16
Nausea.....	15
Syncopc.....	12
Vertigo.....	9
"Excessive gas on stomach".....	6
Emesis of old food (not blood).....	5
Emesis of bright red blood.....	5
Profuse perspiration.....	4
Diarrhea.....	4
Shortness of breath.....	3
Thirst.....	3
Headaches.....	1
Abdominal distention.....	1
Severe chest pain with pain down left arm.....	1
Anorexia.....	1
Feverish.....	1
Double vision.....	1

that he will have recurrence of bleeding. For this reason we are strong advocates of a strict medical regimen which includes adequate follow-up supervision.

The clinical picture at the onset of gastroduodenal hemorrhage varies according to the amount of blood lost. A patient who does not lose more than 350 cc. of blood into the intestinal tract usually does not experience any marked symptoms since the temporary loss in blood volume is quickly compensated for. A patient with such a small loss of blood will experience tarry stools, probably hematemesis of a small amount of blood and will possibly complain of nausea. A patient experiencing a sudden hemorrhage greater than 350 cc. of blood may have hematemesis, an urge to defecate, weakness, nausea, marked perspiration, vertigo and syncope.

If the hemorrhage ceases, these mild symptoms of shock are usually easily overcome. In massive hemorrhages there is, in addition to these findings, evidence of

severe shock with a marked fall in blood pressure, rapid thready pulse, cold and clammy skin, air hunger, marked thirst, anxiety and restlessness. In some patients the loss of blood may be massive yet so slow that the initial complaints are marked weakness, palpitation on exertion and marked pallor of the skin.

Rafsky and Weingarten⁵ have advised grading the severity of bleeding according to the lowest recorded hemoglobin value and red blood cell count in each case. If there was overlapping of the values into two grades, the final classification was based on clinical data such as vertigo, syncope, pulse rate, blood pressure, serum proteins, blood urea nitrogen and the amount of bleeding observed during the hospital stay. The classification as used by these authors was as follows:

Grade of Bleeding	Hemoglobin	Red Blood Cells per cu. mm.
Grade I.	12 Gm. (80%) or above	4,000,000 or above
Grade II.	9-11.8 Gm. (60-70%)	3,000,000 to 3,990,000
Grade III.	6.8-8.8 Gm. (45-59%)	2,250,000 to 2,999,000
Grade IV.	below 6.8 Gm. (below 45%)	below 2,250,000

Such criteria obviate use of such terms in classifying bleeding as profuse, gross, copious and massive, thereby making for a standard with which to judge bleeding.

Using the Rafsky-Weingarten classification of hemorrhage, we obtained the following results:

TABLE X
CLASSIFICATION OF FIRST HEMORRHAGE IN MALES

Grade of Bleeding	No. Patients	Percentage
1	6	18.18
2	9	27.27
3	9	27.27
4	7	21.21
?	2	6.06

In two cases no data were available.

TABLE XI
CLASSIFICATION OF SECOND HEMORRHAGE IN MALES

Grade of Bleeding	No. Patients	Percentage
1	3	25.00
2	5	41.66
3	2	16.66
4	2	16.66

There was one male patient who experienced his fourth hemorrhage and this latter episode was a grade III bleeding.

TABLE XII
CLASSIFICATION OF FIRST HEMORRHAGE IN FEMALES

Grade of Bleeding	No. Patients	Percentage
1	2	20.00
2	3	30.00
3	2	20.00
4	2	20.00
?	1	10.00

In one case no data were available.

TABLE XIII
CLASSIFICATION OF SECOND HEMORRHAGE IN FEMALES

Grade of Bleeding	No. Patients	Percentage
1	1	14.28
2	4	57.14
3	1	14.28
4	0	0.
?	1	14.28

In one case no data were available; one female patient bled six times; no data were available for the third, fourth and fifth hemorrhages and the sixth hemorrhage was classified grade I.

TABLE XIV
CLASSIFICATION OF ALL GROUPS COMBINED

Grade of Bleeding	No. Patients	Percentage
1	13	19.40
2	21	31.34
3	15	22.38
4	11	16.41
?	7	10.44

No data were available for seven cases.

We wish to stress the fact that a patient may enter the hospital with a history pointing toward a recent gastroduodenal hemor-

rhage and yet the initial red blood cell count, hemoglobin and hematocrit may be within normal limits. The laboratory data should not lull one into a sense of false security and make the clinician believe that the hemorrhage was very small for if

TABLE XV
COMPLICATING DISEASES IN OUR PATIENTS

Disease	No. Patients
Secondary anemia	52
Undernutrition	10
Obesity	9
Hemorrhoids	8
Varicose veins of legs	4
Osteoarthritis, generalized	4
Diverticulosis of colon	3
Pyorrhea	3
Chronic cholecystitis and cholelithiasis	3
Hypertension	3
Inguinal hernia	3
Arteriosclerotic heart disease	3
Pulmonary emphysema	2
Diabetes mellitus	2
Menopausal syndrome	2
Hypertensive heart disease	2
Acute appendicitis	2
Central nervous system (lues treated adequately)	2
Incisional hernia	1
Arrested pulmonary tuberculosis	1
Chronic sinusitis	1
Acute glomerulonephritis	1
Chronic tonsillitis	1
Senile dementia	1
Generalized arteriosclerosis	1
Benign prostatic hypertrophy	1
Cerebral arteriosclerosis	1
Varicocele	1
Chronic bronchitis	1
Cataracts	1
Hydrocele of the cord	1
Rectal ulcer (benign)	1
Optic atrophy	1
Prolapse of uterus	1
Polyp of sigmoid colon	1
Cervicobrachial fibrositis	1
Tuberculous adenitis	1
Rheumatic heart disease	1

the laboratory work is repeated within twelve to eighteen hours a marked fall in the values for red blood cells and hemoglobin will often be noted. This is accounted for by the fact that after the initial hemorrhage there has been hemoconcentration and after this has disappeared the blood count, hemoglobin value and hematocrit fall as a result of hemodilution. Some of our patients who presented initial hemocon-

centration proceeded to have a massive hemorrhage while in the hospital, and if adequate blood had not been provided and kept in readiness as soon as the patient entered the hospital, several fatalities might have resulted.

Bockus⁶ has shown that hyperazotemia in massive gastroduodenal hemorrhage may result from absorption of the products of digestion of blood proteins or from functional renal impairment. Alimentary hyperazotemia may be used as a gauge of the severity of bleeding in the absence of vomiting or functional renal hyperazotemia. Azotemia expresses the amount of blood protein absorbed from the bowel and parallels the extent of anemia. The maximum rise in the blood urea nitrogen takes place in twenty-four to forty-eight hours after a massive hemorrhage and returns to normal in seventy-two to ninety-six hours if the bleeding has ceased and the kidney function is not impaired.

Fever and toxic symptoms may be noted in hyperazotemia of alimentary origin between the second and fifth day if a large amount of blood is present in the intestine. Functional renal impairment may result in hyperazotemia not due to the absorption of blood protein from the intestines or intrinsic renal disease. Dehydration contributes to the increase in blood urea nitrogen by bringing on oliguria and anuria. A steady fall in the volume of urinary output with adequate fluid intake indicates marked functional impairment of the kidneys and is a bad prognostic sign. The mortality from hemorrhage is high when the blood urea nitrogen is above 100 mg. per cent. The blood urea nitrogen was determined in fifteen of our patients and the average was 54.1 mg. per cent, a value of 14.1 mg. per cent above the highest normal for our laboratory.

The plasma chlorides may be normal or increased in patients not having excessive vomiting. The blood chloride concentration in such cases is influenced mainly by the degree of dehydration. In six of our patients the plasma chlorides were determined and

averaged 559 mg. per cent (normal 550 to 650 mg. per cent).

Other biochemical changes noted in upper gastrointestinal tract bleeding are: hypoalbuminemia, urobilinogenuria, hyperbilirubinemia and a slight icterus, probably a result of an increase in the activity of the reticulo-endothelial cells. Bockus⁶ states that the hematocrit is very important as an estimate of the magnitude of hemorrhage, as it will be low after hemorrhage and after the hemoconcentration has been corrected. Seven of our patients revealed an average hematocrit of 23.71 per cent. After hemorrhage the healthy bone marrow may respond with varying degrees of leukocytosis, the average count after gastrointestinal hemorrhage being about 12,000 leukocytes per cu. mm. The average white blood count in forty-six of our subjects was 9,447. The bleeding and coagulation time, prothrombin time and bromsulfalein tests were not performed routinely on our patients but all these tests are normal in the presence of bleeding from a peptic ulcer, except for the coagulation time which is accelerated.

Examination of the stools revealed the following data: Forty-five patients had 4 plus occult blood, in twelve cases no stools were sent to the laboratory and in four instances the stools were negative for occult blood at the time the patient was first seen. An attempt was made to determine the number of days it took from the time of entrance to the hospital until the stool became negative for occult blood. The following results were tabulated:

TABLE XVI

Cases	Days	Cases	Days	Cases	Days
1	2	1	11	1	19
1	5	1	14	1	20
2	6	1	15	1	21
1	8	1	16	1	30
3	9	1	17		
2	10	3	18		

Twenty-one patients were not followed adequately so the exact number of days for the stools to become negative for occult blood was not determined.

At the present time it is our policy not to determine immediately the amount of free hydrochloric acid in the case of a bleeding peptic ulcer because it is not always safe to carry out intubation after a recent upper gastrointestinal hemorrhage for fear of precipitating a gastric hemorrhage or rupturing esophageal varices in cases in which the diagnosis may be questionable. Of the cases reviewed a small number of patients did have a free hydrochloric acid determination before we realized the possible dangers resulting from this procedure. The results were as follows:

TABLE XVII

Degrees of Free Hydrochloric Acid	No. Cases
Trace (exact amount not stated)	4
6.....	1
7.....	1
17.....	1
18.....	1
30.....	2
52.....	1
Degrees not stated.....	11

No determination of free hydrochloric acid was done in thirty-six cases.

Serologic study is always important in determining if an upper gastrointestinal lesion is on a luetic basis since most patients with syphilis of the stomach have positive tests. In our series of reviewed cases there were fifty negative blood serology tests. Five were not done, two patients had previously had positive Kahn and Kline tests, had received adequate antiluetic therapy and were serologically negative upon entering the hospital. One patient had 4 plus Kahn and Kline tests on entrance to the hospital.

It has been our policy to hospitalize our patients as soon as we suspect that there has been blood loss into the bowel. Without further delay a careful history is taken and a thorough physical examination is completed, avoiding excessive palpation of the abdomen. The patient's blood is immediately typed and cross-matched so that blood can be made available in large amounts at any hour of the day.

In addition to this the following laboratory data are obtained: (1) red and white blood cell counts; (2) hemoglobin determination; (3) differential count; (4) serology; (5) urinalysis and (6) a hematocrit in many cases. A stool specimen is sent to the laboratory for complete analysis. If the hemorrhage has been profuse, an initial blood chloride and blood urea are usually determined. A blood platelet count, prothrombin determination, bleeding and coagulation times and a bromsulfalein test are performed if we suspect the cause of bleeding to be a result of a hematologic disturbance or combined spleen and liver disease.

Our plan of medical treatment consists of feeding the patient immediately, giving him a Sippy diet with aluminum hydroxide as the antacid. In addition the patient is given supplements of vitamins plus broiled hamburger or scraped beef twice a day. After a period of one to two days supplementary feedings are added in order to increase the patient's caloric intake. By means of this diet we attempt to keep the patient from loading his stomach to an excess at any one feeding yet he is given enough food to satisfy his hunger and to allow for an adequate caloric and vitamin intake. By following this procedure the free hydrochloric acid is diluted and motor activity of the stomach reduced. Early feeding was advocated in 1904 by Lenhartz⁹ who gave his patients milk and eggs from the time of admission and scraped beef on the sixth day. He noted that the body depletion and anemia were overcome more rapidly by this means.

Later Andresen¹⁰ recommended immediate feeding using gelatin mixtures. With this regimen, there was a reduced mortality in his patients with gastrointestinal bleeding. LaDue,¹¹ using Andresen's diet, noted a sharp decrease in the mortality in the patients treated by this method. Early feeding became popular in this country after 1933 when Meulengracht¹² advised a diet of early and liberal feedings. It was thought that the regenerative processes were promoted, the patient became stronger, the

anemia was overcome and the mortality and morbidity were decreased.

We are strong advocates of the policy of transfusing only when indicated by the patient's clinical and laboratory findings. Patients who have grade I bleeding obviously do not need a transfusion providing that the bleeding ceases soon after the patient enters the hospital. Patients with grade II bleeding may or may not need blood. We usually begin to administer small transfusions whenever the hemoglobin has fallen to approximately 10.5 Gm. and the red blood cell count to 3,750,000. Patients with grade III and grade IV bleeding are routinely transfused. When no emergency exists the blood is given slowly, usually in the amounts of 250 cc. per transfusion and is repeated until the blood determination reaches a hemoglobin of 12 Gm. and 4,000,000 red blood cells.

An occasional patient may go into shock so rapidly that the blood must be given quickly to avoid irreversible tissue changes. Such subjects may be given plasma until blood becomes available. With this type of case, blood is given until the patient is no longer in shock as judged by clinical criteria after which small transfusions are resumed. An occasional patient may continue to bleed slowly so that life-endangering exsanguination may take place. In both the slowly and rapidly bleeding patients falling into group IV we have given up to 1,000 cc. of blood over a twenty-four-hour period for from one to two days. We do not hesitate to exceed this amount if necessary.

Blood transfusion for bleeding ulcer has always been and remains a controversial subject. Those who advocate no blood unless the red blood cell count is 2,500,000 or less maintain that transfusions will raise the patient's blood pressure and dislodge any clots that may have formed at a bleeding point, thereby increasing the extent of the hemorrhage. Those clinicians who advocate early transfusions believe that there is no danger either in the amount or the rate of transfusion. Böhrer⁷ in his series of cases stated that transfusions were given for

massive gastric hemorrhage in the amounts of 500 to 1,000 cc. and that no secondary hemorrhages were noted.

Jones¹³ has administered slow transfusions in amounts up to 2,650 cc. daily, without a rise in the blood pressure. Since massive upper gastrointestinal bleeding tends to cause hypoproteinemia, blood transfusions are given to replace the valuable proteins and the red blood cells tend to overcome tissue anoxemia, both factors playing a large part in preventing further bleeding by aiding tissue healing. Recently Levy¹⁴ has called attention to the importance of hypoproteinemia resulting from bleeding peptic ulcer and has noted a beneficial effect from the administration of amino acids.

In addition to the diet and blood therapy, sedation is used routinely but the amount varies. On the type of diet which we have recommended the patient receives $\frac{1}{4}$ gr. (0.016 Gm.) of luminal three times a day in combination with belladonna.

If an excessive amount of retching occurs or the patient is unduly restless and apprehensive, sodium luminal is given intramuscularly in the dose of 2 gr. (0.13 Gm.) every three to four hours as needed. Morphine and other narcotics have not found favor with us because of the frequently associated nausea, vomiting and anorexia which follows.

Considerable attention must be given to the bowels inasmuch as our diet is very constipating. A small saline enema is given every second to third day. In addition to avoiding fecal impaction this will rid the bowel of the broken-down digestion products of the old blood which many clinicians believe cause a toxic reaction and fever in the first three to five days of the illness. Emphasis is placed upon the fact that psychotherapy is a very important and integral part of treatment in any type of ulcer patient but particularly so with the patient with a bleeding ulcer who frequently is very apprehensive and under great stress.

We present the following three histories to illustrate the application of our medical regimen which has been described. It should

be noted that these patients were extreme examples of grade iv bleeding who were very difficult to handle. Emphasis is placed on the part played by early feeding plus large amounts of blood in achieving successful therapy.

CASE REPORTS

CASE I. M. B., a male, was first seen on May 27, 1945, at which time he stated that he had had "stomach trouble" for one month. The onset of his illness was characterized by midline epigastric pain and gaseous distention. The pain appeared about one-half hour after eating and was relieved by milk of magnesia or sodium bicarbonate. The abdominal pain radiated to his back and the vicinity of the right scapula. He was seen by a doctor who made a diagnosis of gallbladder disease for which he was treated. He appeared to improve on a medical regimen when suddenly two days before being hospitalized while at work he vomited what he believed to be 1 pint of dark red blood. He then developed the back pain but no longer had the epigastric distress. One day prior to entering the hospital he again had a sudden emesis of what he believed to be 1 pint of dark blood. He had lost 10 pounds of weight in five weeks. The patient was immediately hospitalized. There was no history of abdominal trauma or excessive indulgence in alcohol. The past history was noncontributory.

Physical examination revealed an acutely ill, undernourished, white male of forty-four years of age. His height was 5 feet 9 inches and he weighed 135 pounds. His skin was warm, dry and had lost its turgor. The rest of the examination was negative.

Laboratory work done upon entrance to the hospital showed the following: urine was negative; hemoglobin was 58 per cent; red blood cell count was 2,750,000; white blood cell count was 5,350 and the color index was 1.05. The differential count revealed 72 per cent polymorphonuclear neutrophils of which 70 per cent were filamented and 2 per cent were non-filamented. There were 28 per cent lymphocytes. The red blood cells showed moderate anisocytosis. The Kline test was negative. The stool specimen was tarry-colored and gave a 4 plus reaction for occult blood. The blood urea was 97.7 mg. per cent, the blood chlorides were 503 mg. per cent and the carbon dioxide com-

binning power was 61 volumes per cent. The bromsulfalein test did not reveal any dye retained at the end of one hour. A chest x-ray revealed a healthy chest.

The patient's course in the hospital was very stormy. He was put on hourly feedings of milk and cream from 7 A.M. to 7 P.M. and again at 2 A.M. and 5 A.M., with supplementary feedings of broiled hamburger twice a day. Atropine gr. $\frac{1}{150}$ (0.0004 Gm.) by hypodermic was given until there was dryness of the mouth and visual disturbances. The patient was also given sodium luminal gr. 2 (0.13 Gm.) intramuscularly every four to six hours. In addition he received large doses of vitamins parenterally. On this regimen he continued to be nauseated and vomited large amounts of dark red blood. With each emesis, he had symptoms of mild shock for which he was given 250 cc. of plasma the first day, 500 cc. of blood the following day and 250 cc. of blood the third day. On the fourth day two blood transfusions of 250 cc. each were administered and on the fifth day he was given 750 cc. of blood. With all this parenteral therapy his laboratory data showed 30 per cent hemoglobin and a red blood cell count of 1,460,000.

Since the situation seemed to be rather desperate for the patient, it was decided to give him large amounts of blood slowly and continuously. On June 1st he was given 1,000 cc. of blood after which he began to feel better, retained his diet and was no longer nauseated. The blood data on this day revealed a hemoglobin of 44 per cent and a red blood cell count of 2,100,000. He was given 500 cc. of blood daily for the next five days and continued to feel well and improve clinically. On the sixth day after this intensive therapy the hemoglobin was 83 per cent and the red blood cell count was 4,120,000. Two days later the patient was up and about. A gastrointestinal x-ray (without abdominal manipulation) on June 13th was interpreted as being suspicious for a small duodenal ulcer. He was discharged from the hospital on June 14, 1945, and has felt well since.

CASE II. S. N., a forty-seven year old male, entered the hospital on February 3, 1945, in a state of shock. He stated that an hour previous to his entrance he had begun to vomit large amounts of dark red blood. He was immediately given 250 cc. of plasma which was followed by 250 cc. of red blood cells suspended in saline. There was a dramatic response and his blood

pressure rose; he became alert and was no longer cold and clammy.

Careful questioning then revealed that for the past three years he had complained of "indigestion" which first began as a midline epigastric cramping pain that began one-half hour after meals. Taking soda bicarbonate and amphogel wafers relieved the pain. The pain never awakened him at night. Since this initial onset of pain, he began to complain of vague abdominal discomfort stating he "bloated" immediately before and after meals. He did not know whether taking food relieved his epigastric pain or not. For the past three weeks he had felt a gradual loss of strength and an inability to do heavy work.

On the day of entrance to the hospital, while at work, he suddenly became very warm, felt nauseated and had an urge to defecate. He suddenly fainted after vomiting dark red blood and when he regained consciousness the vomiting of dark red blood began again. There was no previous history of tarry stools nor was there any history of consumption of an excess of alcohol. The patient had been treated adequately for syphilis; otherwise, the past history was non-contributory.

Physical examination upon entrance to the hospital revealed the following: the patient was 5 foot 8½ inches tall and weighed 145 pounds. His pulse rate was 120 and his blood pressure 70/50. He was very restless and his skin was cold and clammy. His lips were covered with fresh blood. His abdomen revealed a slight tenderness in the epigastric area but there was no rigidity. The liver, spleen and kidneys were not palpable.

Laboratory data revealed the following: Hemoglobin was 65 per cent (10 Gm.); the red blood cell count was 3,360,000, the white blood cell count was 17,200 and the color index was 0.99. The differential smear revealed 76 per cent polymorphonuclear cells, 53 per cent being filamented and 23 per cent non-filamented, 23 per cent lymphocytes and 1 per cent monocytes. The urine was negative as was the Kline test. The blood urea was 113 mg. per cent, the blood chlorides were 578 mg. per cent and the carbon dioxide combining power was 50 volumes per cent.

The patient was put on the same diet as was used in Case I, with adequate vitamins. No gastric analysis was carried out. The patient felt well until 4:30 P.M. on February 4th when he suddenly began to vomit large amounts of

dark blood, his skin became cold and clammy and he had a desire to defecate. His stools were tarry. The patient was immediately given 500 cc. of plasma and 500 cc. of whole blood but his condition did not improve. He continued to vomit, his skin was cold and clammy and his bladder and bowels were incontinent. Because of the gravity of the situation, it was decided to place a No. 18 gauge needle in each antecubital vein and to administer whole blood and saline suspensions of red blood cells continuously. The patient received 1,500 cc. of whole blood throughout the night and was given 2,300 cc. of whole blood and 300 cc. of red blood cell suspension during the following day. At approximately 6 P.M. (on February 5th) a marked improvement was noted in his condition. His blood pressure had risen to 108/72 but his pulse continued at a rate of 120 per minute. He was having frequent tarry stools but could retain his diet. Laboratory data revealed a hemoglobin of 60 per cent (9.3 Gm.), 3,480,000 red blood cell count and a hematocrit of 29 per cent.

Because of the marked anemia, he was given 400 cc. of red blood cell suspension on February 6th. On this same date there was a rise of temperature to 104 degrees and a diagnosis of pneumonia was made clinically and by x-ray. Recovery was successful with sulfadiazine therapy. On the following day the patient received 1,000 cc. of red blood cells and transfusions were continued the next day in the amount of 500 cc. of red blood cells. The last three transfusions were given slowly as there was no emergency. On February 8th, the last day of transfusions, his hemoglobin was 80 per cent (12.5 Gm.) and the red blood cell count was 4,280,000. The blood urea had fallen to 36.3 mg. per cent. The patient was discharged from the hospital on March 13, 1945, and has continued to feel well since.

CASE III. W. M., a male, was brought to the hospital on October 6, 1945, and gave the following history: Approximately eight years before he noted tarry stools and was told that he had a gastric ulcer. He responded well to conservative medical therapy. Three months previous to entering the hospital he had a cholecystectomy from which he made an uneventful recovery. About two months ago the patient began to develop cramp-like pains in the lower abdomen and also in the epigastrium. He did not recall if the pains were noted after meals or

if they were relieved by food or alkali. He also noted excessive flatulence.

Two days before admission to the hospital the patient observed tarry stools of one day's duration. He also had been experiencing double vision and weakness for the past two days. On the day of admission he had vomited dark red blood. The patient also remarked that for the past month he had become increasingly nervous. The past history revealed that he had received adequate antiluetic therapy fifteen years previously.

Physical examination revealed the following: the pulse rate was 110 and the blood pressure 88/58. The patient was an obese white male of fifty-five years of age who was very pale and appeared restless. His pupils reacted to accommodation but not to light. The abdomen revealed slight epigastric tenderness. Laboratory data upon admission to the hospital revealed examination of the urine to be negative, a hemoglobin of 54 per cent and a red blood cell count of 3,000,000.

This patient was also put on a dietary regimen as described in Case I, plus adequate vitamins. No gastric analysis was done at this time but an Ewald test meal one year previously showed 24 degrees free hydrochloric acid. In addition small transfusions of 200 to 350 cc. of blood were slowly administered daily. On the third day of hospitalization after receiving 950 cc. of blood the blood count was 46 per cent hemoglobin and 2,250,000 red blood cells. On the following day it was decided that the patient's condition was becoming worse and therefore larger transfusions, each averaging 500 cc., were given. On October 15th, after receiving a total of 2,250 cc. of blood, the blood count was 2,260,000 red blood cells and 46 per cent hemoglobin. The patient was having tarry stools daily. The same day small transfusions of 250 cc. daily were resumed but by five days later the hemoglobin had fallen to 35 per cent and the red blood cell count was 1,960,000 in spite of an additional 1,000 cc. of blood.

Because of the patient's critical condition, it was deemed necessary to give him large amounts of blood. As a consequence a No. 18 gauge needle was inserted into the vein of the left antecubital fossa and whole blood was ordered continuously with at least 1,000 cc. to be given within the first twenty-four-hour period. On October 23rd, after receiving 1,500 cc. of blood, the patient's hemoglobin was 74 per cent with

a red blood cell count of 3,920,000. For the first time since entering the hospital his stools were brown and he felt well. In view of the fact that the emergency had passed it was decided to discontinue giving blood around the clock and the patient received his last transfusion of

TABLE XVIII
NUMBER OF HEMORRHAGES PER PATIENT*

Sex	No. Hemorrhages	No. Patients
Female.....	1	9
Female.....	2	7
Female.....	3	1
Female.....	4	1
Female.....	5	1
Female.....	6	1
Male.....	1	31
Male.....	2	12
Male.....	3	1
Male.....	4	1

* Includes patients with multiple hemorrhages.

TABLE XIX
AMOUNT OF BLOOD GIVEN FOR EACH HEMORRHAGE

Sex	No. Hemorrhages	No. Patients Receiving Transfusions	Total No. Transfusions	Average Amount of Blood per Transfusion per Patient	Average Amount of Blood Received per Patient
Female.....	1	6	12	310 cc.	620 cc.
Female.....	2	5	28	305.35 cc.	1710 cc.
Female.....	3	0	0	0	0
Female.....	4	0	0	0	0
Female.....	5	0	0	0	0
Female.....	6	0	0	0	0
Male.....	1	25	105	453.80 cc.	1906 cc.
Male.....	2	7	51	366.66 cc.	2671.42 cc.
Male.....	3	0	0	0	0
Male.....	4	0	0	0	0

500 cc. on this date. A week later the hemoglobin was 81 per cent with a red blood cell count of 4,310,000. The patient was discharged on November 3, 1945, and adequate follow-up has indicated that he has had no difficulties since leaving the hospital.

A total of forty-seven series of transfusions was given to our patients: forty-six of these were administered slowly and one series was administered rapidly to begin with, after which small, slow transfusions were given.

There were four male patients who received plasma infusions. These patients were all experiencing their first hemor-

rhages. A total of six infusions was given, the total amount of plasma per infusion being 250 cc. and the total amount of plasma received per patient was 375 cc.

In analyzing our data presented in Tables XVIII, XIX and XX a total of 196

TABLE XX
AMOUNT OF RED BLOOD CELLS GIVEN PER HEMORRHAGE*

Sex	No. Hemorrhages	No. Patients Receiving Transfusions	Total No. Transfusions	Average Amount of Red Blood Cells per Transfusion	Average Amount of Red Blood Cells Received per Patient
Female.....	1	1	6	250 cc.	1500 cc.
Female.....	2	1	4	250 cc.	1000 cc.
Female.....	3	0	0	0	0
Female.....	4	0	0	0	0
Female.....	5	0	0	0	0
Female.....	6	0	0	0	0
Male.....	1	4	12	537.5 cc.	1612.5 cc.
Male.....	2	0	0	0	0
Male.....	3	0	0	0	0
Male.....	4	0	0	0	0

* Red blood cells administered as a saline suspension.

transfusions were administered for an average of 358.95 cc. per transfusion. This exceeds the average size transfusion of 250 cc. which is usually recommended. Since some of our patients were in shock and others entered the hospital markedly anemic, it was deemed necessary to give larger transfusions than the average. The average total amount of blood received per patient in our series equaled 1,726.85 cc. whole blood. The average size red blood cell transfusion was 471.05 cc., and the average total of red blood cells received per patient was 1,325 cc. In the case of one patient it was necessary to give 2,450 cc. of red blood cells, 4800 cc. of whole blood and 750 cc. of plasma. The average red blood cell count per patient at the time of discharge from the hospital was 4,266,153 and hemoglobin 69.6 per cent (10.08 Gm.)

There is considerable debate as to whether emergency surgery should be performed on the patient with a massive hemorrhage from a peptic ulcer. Bockus⁶ states that most clinicians prefer to follow the advice of Rodman who recommended that surgery not be performed during an active hemorrhage, with rare exceptions.

The latter author thought that surgery was contraindicated since no definite diagnosis was usually made at the time of the hemorrhage and, therefore, that surgery was usually of no avail. He also believed that the patient who had a severe hemorrhage was a poor surgical risk and pointed out that recovery is frequently the rule without surgery.

Finsterer, quoted by Bockus,⁶ has been an advocate of surgery in the case of bleeding from the upper gastrointestinal tract. He operated upon seventy-eight patients who were good risks, defining the latter as those patients operated upon twenty-four to forty-eight hours after the initial bleeding began. He performed a subtotal gastric resection in seventy-one of his patients with four deaths (5.41 per cent mortality). He also performed subtotal gastric resection in sixty-three patients who had bled, the operation being performed forty-eight hours or longer after the initial hemorrhage. In this series of cases the mortality rose to 26.9 per cent. Those who have analyzed Finsterer's statistics have thought that the latter series would have yielded better results with medical management inasmuch as not more than 10 per cent of the patients with massive hemorrhage will usually die after medical treatment. As for low mortality in the cases of early bleeding it is unwise to subject all such patients to surgery since many may be easily controlled with medical management. Bockus⁶ believes that individualization in the selection of patients submitted to surgery is important. He advocates use of conservative therapy for a brief period of time and if the hemorrhage has been severe, the normal blood volume cannot be maintained and all the signs point toward continued bleeding then surgery must be considered. If such a patient is fifty years of age or older and gives a long history of ulcer symptoms, then additional weight is given in favor of surgical intervention. He also believes that patients who have an exacerbation of their severe hemorrhage several days after a first hemorrhage should be

submitted to surgery if it is not possible to maintain their normal blood volume.

Held¹⁵ believes that elective surgery should not be carried out after only one hemorrhage unless the patient must be away on long journeys from a place where he could safely obtain adequate medical or surgical care. A second hemorrhage within six months to a year is sufficient ground to advise surgical intervention after the second hemorrhage. After a third hemorrhage surgery should be carried out regardless of circumstances. Surgery is also recommended if occult blood appears in the stool intermittently and in sufficient quantities to account for a secondary anemia. In the latter case it is believed that frequent oozing should make one suspicious of the development of a malignant lesion. Moreover, the continued bleeding from the ulcer lowers the tissue resistance so that healing becomes impossible and perforation may take place.

Hunt¹⁶ believes that patients who are fifty years of age or older and who have recovered from a massive hemorrhage should be subjected to surgery. In our series no patients were treated surgically for bleeding from the upper gastrointestinal tract. No female patient had any form of surgery of the stomach or duodenum previous to her hemorrhage. Two male patients had gastroenterostomies, one male had a pyloroplasty and one patient had emergency surgery for closure of a ruptured gastric ulcer before the hemorrhage. It is of interest to note that two of our male patients had massive hemorrhages three months after a cholecystectomy.

The mortality figures collected from various clinics and hospitals in this country and abroad are not adequate to establish a definite mortality figure. In some statistical papers many cases may be excluded since there is doubtful evidence of peptic ulcer. In other cases only massive hemorrhages have been reported with a high mortality, whereas other authors have recorded only episodes of minor bleeding. There is some general agreement in the mortality statistics from large city hospitals where only massive

hemorrhages were considered. The mortality in such cases is roughly 10 per cent. The mortality figures for ulcer hemorrhages are also unreliable since some clinicians have excluded certain fatalities from their lists for various reasons.⁶

The following factors influence the prognosis of massive hemorrhage from the gastrointestinal tract:

(1) It has been noted that there is a much lower mortality in bleeding ulcers in the female. (2) The age factor is one of the most important in determining the outcome for the patient, most deaths occurring after the age of forty-five. (3) There is a definite higher incidence of deaths from first hemorrhages. In one series 78 per cent of the deaths were reported to have resulted from the first hemorrhage.¹⁷ (4) Antecedent dyspepsia or ulcer-like symptoms definitely give a worse prognosis for bleeding ulcer patients. It has been suggested that in those without previous ulcer symptoms the bleeding is due to a superficial ulcer or erosion rather than to a deep ulcer. (5) Arteriosclerosis is stated to be a definite factor in the prognosis since the older patients bleed from ruptured, stiff vessels which do not retract and tend to stop bleeding. (6) It has been stated that a patient showing a blood urea nitrogen of 100 mg. per cent or more or those patients in whom the loss in cell volume exceeds 50 per cent the prognosis is definitely worse.⁶ (7) Hypertension. (8) Erosion into the pancreas and bleeding from granulation tissue in the base of the ulcer have been stated by Schenken¹⁸ to be definite factors in giving a worse prognosis in these cases.

COMMENTS

Fifty-seven cases of bleeding from the upper gastrointestinal tract without a death have been presented. These represented all the case records available to us in which the cause of the bleeding was considered to be benign peptic ulcer. The diagnosis in each case was consistent with peptic ulcer as determined by x-ray and/or clinical and laboratory data. The patients considered were either seen for their initial hemorrhage

or were being treated for a repeated episode of bleeding.

In the case of twelve patients no x-rays were taken but previous x-rays had been taken elsewhere and the results were made available to us. Eight patients had negative x-rays but had been on strict ulcer management for two weeks or more so that healing probably had taken place.

The combined age incidence of both the men and women in our series at the time of onset of their hemorrhage, either as an initial or repeated incidence, shows that sixty-one hemorrhages took place when the patient was in the age group of forty years or older.

Using the Rafsky-Weingarten classification for the severity of hemorrhage, it will be noted that twenty-six or 43.33 per cent of our patients had grade III or IV bleeding which is a massive hemorrhage. Forty of our patients had hemorrhages for the first time. The average duration of gastrointestinal symptoms was 5.64 years for the males and 7.6 years for the females. Taking all these factors into consideration, one would certainly expect some fatalities. Again we wish to stress the fact that if the red blood cell count falls to 3,750,000 and the hemoglobin to 10.5 Gm., we give small transfusions of 250 cc. until the hemoglobin is 12 Gm. or greater and the red blood cell count is 4,000,000 or greater. If the patient enters in or develops shock while in the hospital, blood is given rapidly until the shock is overcome; then small transfusions are resumed as long as there is no emergency and the patient maintains his blood volume. If the patient continues to lose blood slowly and this is not replaced by small transfusions, then large amounts of blood are given slowly until the patient's blood volume is maintained at a high level, after which small transfusions are continued.

CONCLUSIONS

1. An analysis of fifty-seven cases of gastroduodenal hemorrhage as the result of peptic ulceration is presented. There were no fatalities in our series. There were thirty-nine patients with duodenal ulcer and

nineteen with gastric ulcer, giving a ratio of 2.05 to 1.

2. Hemorrhage from peptic ulceration may take place at any age but it occurred more frequently in the fourth and fifth decades of life in our series. This has been the observation of other clinicians.

3. Bleeding from the upper gastrointestinal tract as a result of benign ulcers occurs more frequently in men than in women. In our series there were forty-two males and fifteen females, a ratio of 2.8 to 1.

4. Body build was not a pertinent factor in the occurrence of ulcer nor was it a factor in predisposition to hemorrhage in the cases reviewed.

5. We strongly advocate that patients with bleeding from the upper gastrointestinal tract not be x-rayed until at least two weeks have elapsed after the onset of their hemorrhage.

6. Factors precipitating gastrointestinal hemorrhage are: (1) upper respiratory infections; (2) alcoholic beverages; (3) emotional disturbances; (4) dietary indiscretions and (4) physical exertion and overwork.

7. The period from October to March is stated to be the time interval during which most hemorrhages from benign ulcer occur. This was confirmed in our series.

8. From an analysis of our figures it is apparent that there is a great tendency for a patient to have repeated hemorrhages after the initial episode of bleeding.

9. Using the Rafsky-Weingarten classification for the grade of bleeding from a peptic ulcer, there were twenty-six cases (43.33 per cent) classified either as grade III or IV bleeding.

10. The biochemical changes noted following gastrointestinal bleeding are (1) alimentary hyperazotemia; (2) hyperazotemia as a result of functional renal impairment; (3) increase in plasma chlorides, (4) hypoalbuminemia, (5) urobilinogenuria and (6) hyperbilirubinemia.

11. We have outlined the management of upper gastrointestinal hemorrhage. Strong emphasis is placed upon early feeding and large amounts of blood when indicated.

Three cases of grade IV bleeding were presented as well as the management and progress of these patients. Continuous and massive blood transfusions are not only life saving but innocuous.

12. We have not had any experience with emergency surgery in bleeding peptic ulcer. Before surgery is attempted we believe that conservative treatment should be carried out.

13. The mortality in bleeding peptic ulcer is determined by the following: (1) sex; (2) age; (3) number of hemorrhages; (4) chronicity; (5) arteriosclerosis; (6) marked elevation of blood urea and decrease of cell volume to 50 per cent or lower; (7) hypertension; (8) erosion into the pancreas and (9) bleeding from granulation tissue in the base of an ulcer.

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Metabolic Studies in Cushing's Syndrome*

Treatment with Various Androgens and a Six-year Follow-up

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IN the sixteen years which have elapsed since Cushing⁵ described the clinical syndrome now bearing his name a considerable volume of literature has accumulated relative to the diagnosis and treatment of this condition. Numerous types of therapy have been advocated. In those instances in which a pituitary or adrenal tumor could be demonstrated surgery has resulted at times in some clinical improvement and occasionally in remission or cure of the disease.³⁶ Similar claims have been made for x-ray therapy applied to the pituitary and adrenals or radon seeds implanted into the sella turcica.²³

Encouraging results have been claimed for estrogens^{4,9,14,22} as well as for androgens.^{1,2} Albright,¹ who originally suggested the use of testosterone propionate, believed that the disease was associated with or caused by a hypergluconeogenesis at the expense of body protein. Many of the clinical manifestations were thought to be the result of decreased protein availability, for example, muscular weakness, thin skin, easy bruisability and osteoporosis. In metabolic studies on three patients he was able to show, among other findings, a negative nitrogen and phosphorus balance as well as increased urinary calcium excretion. Because of its ability to cause storage of nitrogen, testosterone propionate was selected as a therapeutic agent and his patients received a trial of this substance. Clinically, there was symptomatic improvement as shown by increase in strength and weight, diminished redness of the skin and

loss of easy bruisability. Furthermore, the patients promptly stored large quantities of nitrogen as well as phosphorus, the excessive excretion of urinary calcium was checked, calcium absorption improved and the balance became positive. Estrogen therapy failed to exert a beneficial effect on nitrogen, phosphorus and calcium balances in two cases.

Perloff et al.²⁴ studied a woman with Cushing's syndrome using calcium gluconate, vitamin D₂, testosterone propionate, estradiol benzoate and diethylstilbestrol. Following administration of testosterone propionate, there was retention of nitrogen and phosphorus but with prolongation of treatment for 123 days the nitrogen excretion returned to approximately control levels. Calcium retention was demonstrated with vitamin D₂ but not with the other steroids used. Subjectively, at the end of the period of study the patient noticed an increase in muscular strength and improvement in backache. Objective findings included deepening of the voice, enlargement of the clitoris, increase in facial acne and hirsutism, amelioration of diabetes and some recalcification of the spine. Deakins et al.⁶ observed retention of nitrogen with androgen therapy but neither with this treatment nor with estrogens was clinical improvement noted. Their periods of treatment were short and the patient did not present all of the findings characteristic of advanced Cushing's syndrome. In White-law's case³⁵ administration of testosterone propionate resulted in increased strength

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but was without effect on hypertension, osteoporosis or calcium excretion.

The purpose of the present paper is to present metabolic data on a young female patient with Cushing's syndrome and to evaluate androgen therapy in the light of six years' observation of the patient.

CASE REPORT

J. D. was a fifteen year old white girl who was admitted to the hospital on July 21, 1941, complaining of backache and of being overweight. (Fig. 1.) She had considered herself well until seven months previously when she first noted some pain in her back after jumping over a wooden horse in gymnasium. Following a brief period of rest, she was symptom-free for about five months when she again complained of backache while carrying a pail of water. Weakness gradually developed in her legs and trouble was experienced in getting in and out of bed. Three days prior to admission while stooping to wash her face she had such intense pain in her back that she screamed.

During the previous two years gain in weight had been rapid. Her first menstrual period occurred six months before admission. This was followed by five months of amenorrhea. After receiving a course of estrogens from her local physician (amount unknown) she had another period one month before admission. She also had noted thinning of the hair on her head as well as some increased growth of hair on her face. She suffered bruises easily and it was her impression that her head and face seemed to have increased in size. She also had noted that her arms and legs seemed disproportionately thin in comparison with the rest of her body.

The patient's past history revealed that she had been born prematurely weighing $4\frac{1}{2}$ pounds at birth; she walked late at the age of twenty-two months. Development was otherwise apparently normal until the onset of gain in weight two years previously. Other members of the family seemed normal except that the mother was quite obese. An older brother and sister were in good health.

Physical examination revealed the following: Temperature 37°C ., pulse 72, respiratory rate 16; blood pressure 146/92; height 148 cm., weight 54.3 Kg. Her general appearance was rather striking; she was obese and appeared older than her stated age. There was excessive



FIG. 1. Patient J. D., aged fifteen, at time of first admission.

rubicundity with a full-moon face and "buffalo" distribution of the obesity as well as a conspicuous roll of fat beneath her chin. The facial hair was excessive while that on the scalp was thin and of fine texture with partially bald areas. The skin was very thin over the extremities with a mottled, cyanotic hue. Over the anterior abdomen, flanks and upper thighs many wide red or purplish striae with smooth, shiny, paper-thin surfaces were seen. The axillary and pubic hair was sparse and coarse; the latter had a male type of distribution. The neck appeared unusually short so that the head seemed to rest on the shoulders. The dorsal kyphos was exaggerated and tenderness was present over the right iliac crest. Weight-bearing was very painful with complaints referable to the lumbar spine. The visual fields and fundi were normal. She had moderately severe dental caries. The breasts were small and poorly developed; the heart, lungs and abdomen were not remarkable; the genitalia were normal for a girl of her age.

Laboratory data revealed the following: Blood Wassermann test, negative. Blood: red blood cell count, 5,900,000; hemoglobin, 19.6 Gm./100 cc.; white blood cell count, 9,200. The differential formula was normal. Stool examination: light brown, formed, guaiac negative. Urine examination: specific gravity, 1.020; albumin 0; sugar, 0. Microscopic examination negative and cultures sterile. Phenolsulfonphtha-

lein excretion test, 90 per cent in two hours. Blood chemistry: whole blood contained non-protein nitrogen, 34 mg.; sugar, 67 mg./100 cc. The serum contained for each 100 ml.: total proteins, 6.2 Gm.; albumin, 4.2 Gm.; globulin, 2.0 Gm.; calcium, 9.3 mg.; phosphorus, 3.6 mg.; alkaline phosphatase, 8.7 Bodansky units; acid phosphatase, 3.5 King-Armstrong units and cholesterol, 261 mg. For each L. of serum there were: chloride, 101 mEq.; carbon dioxide, 26 mEq. and potassium, 4.3 mEq. (For sugar tolerance tests, urinary neutral 17-ketosteroids, creatine and creatinine and basal metabolism *vide infra*.) The results of a glucose insulin tolerance test¹² were as follows:

Time (min.). Fasting	20	30	45	60	90	120
Blood sugar						
(mg. per						
cent).....	95	156	155	154	151	142 118

Follicle-stimulating hormone: less than five mouse uterine units per twenty-four hours.³²

Microscopic examination of uterine curettings and skin: The pelvic examination was done under anesthesia. The cervix and uterus were unusually small. Curettings revealed a resting endometrium. Biopsy of the skin of abdominal stria: "Normal skin thins out gradually with lessening of elastic fibrous tissue until hardly any elastic tissue is present. Few skin glands are seen."

X-ray reports revealed that the sella turcica was not enlarged in two examinations. There was decalcification of the bones of the forearms, lumbar spine and pelvis with collapse of the vertebral bodies of the lower dorsal and upper lumbar spine. Bilateral perirenal air insufflation did not reveal enlarged adrenals. No abnormality of the renal pelvis was found by retrograde pyelography.

On September 13, 1941, she was transferred to the metabolic unit for the purpose of investigating the effects of androgens (*vide infra*). Following this she was given additional daily injections of testosterone propionate. Because of the severe osteoporosis of the spine and resulting pain in the back, abdomen and thighs, she was confined to bed most of the time at first but by February, 1942 was able to be up part of the day. Late in September, 1941 she began to have blurring of vision and ocular pain, occasional at first but gradually increasing, until by May, 1942 the existence of chronic glaucoma was definite. In June a bilateral

Elliott trephine operation was carried out which relieved her symptoms considerably.

She was discharged on November 21, 1942, having received 4,865 mg. of testosterone propionate intramuscularly. Pains had subsided somewhat but her blood pressure had increased to an average of 190/130, marked hypertensive changes had occurred in the retinal vessels and headaches were more pronounced. Her weight was the same as on admission. She was able to go to school. A large part of the time between this and the next admission she received methyl testosterone, 30 mg. daily.

In August, 1943 she developed auricular fibrillation. Her weight had increased 6 Kg. and a small amount of protein was now found in the urine. She was digitalized and the auricular fibrillation ceased. Perirenal air injections were repeated but failed to show an increase in the size of the adrenals. Because of gradually increasing polycythemia with hematocrit levels of 52 to 56 per cent, phlebotomies were carried out at various subsequent intervals. After discharge she was able to return to school for a very brief period.

In May, 1944 she was hospitalized again because of increasing upper abdominal pain. During this admission there was 2 plus albuminuria and a few red and white cells were found in the urinary sediment. Phenolsulphonphthalein excretion was 25 per cent and in thirty minutes, 50 per cent in two hours. Non-protein nitrogen ranged from 25 to 30 mg. per cent. Exploration of both suprarenal regions were performed by Drs. J. J. Morton and E. B. Mahoney. The adrenals were not enlarged and sections were interpreted by most observers as showing hyperplasia of the cortex. The ovaries and uterus were found to be very small.

After discharge in July she was given 30 mg. of methyl testosterone and 1 mg. of alpha-estradiol daily for about four months, and approximately every three months phlebotomy was performed which temporarily relieved the polycythemia and headache. However, the blood pressure remained around 200/130 and the weight gain continued.

When she was next admitted in April, 1945, her weight was 72 Kg. She was placed on the rice and raisin diet advocated by Kempner,²⁰ with a caloric intake of between 800 and 1,000 calories. During the first two months on this regimen she felt better than she had in some years and her blood pressure had decreased (150-170/100-100). During ninety days she

lost 17 Kg. Rather suddenly thereafter she became very weak, fainted several times and it was found that her serum proteins had decreased to 5.1 Gm. per cent from previous levels of 6.4 Gm. per cent to 7.1 Gm. per cent. The diet was changed to one liberal in proteins and low in calories and she was discharged in August. For two months thereafter she felt much improved and was able to visit relatives in the mid-west.

In November, 1945 she had frequent and prolonged epistaxes. She was markedly anemic and was found to have a urinary tract infection. A urea clearance was 50 per cent of normal on two occasions; blood non-protein nitrogen was 35 mg. per cent; the blood pressure was 205/120.

In February, 1946 she was admitted for treatment of the urinary tract infection with penicillin. The blood pressure was 205/140. In June it was necessary to admit her again because of epistaxes and from this time until her death her arms and legs were continually covered with bruises and ecchymoses.

In December, 1946 the blood pressure was 210-240/150 and a pulsus alternans was noted at times. Blood non-protein nitrogen was 37 mg. per cent, fasting blood sugar 76 mg. per cent and hematocrit 47 per cent. In March, 1947 she was brought in because of extreme dyspnea, insomnia, failing vision, epistaxis and back pain. Her face was fiery red and her stature shorter than before. She had advanced hypertensive retinopathy, cardiac hypertrophy, tachycardia, a gallop rhythm but no signs of congestive failure. The urine contained albumin, red cells, leukocytes and casts. The blood urea nitrogen was 50 mg. per cent and the glomerular filtration rate, determined by Dr. C. Waterhouse, was 17 ml. per minute. Treatment consisted of digitalization and a low salt, low protein diet. The blood pressure dropped slightly and she lost some weight. After two weeks she wished to return home and was discharged on this regimen.

Two weeks later she entered the Community Hospital, Warsaw, N. Y. and Dr. P. A. Burgeson was kind enough to furnish us with the following data: The blood non-protein nitrogen was 59 mg. per cent, serum calcium 8.5 mg. per cent and phosphorus 4 mg. per cent. A glucose tolerance test was as follows: Fasting specimen 95 mg. per cent, one-half hour 145 mg. per cent, one hour 165 mg. per cent, two hours 170 mg. per cent, three hours 150 mg. per cent. Radio-

graphs of the skull showed expansion and deepening of the sella turcica with erosion of the posterior clinoid processes. Two weeks after admission the blood non-protein nitrogen had risen to 117 mg. per cent and one week thereafter, shortly before death, it was 168 mg. per cent. It was decided that the patient's death was due to renal failure and uremia.

An autopsy was performed by Dr. J. Tannenbergh of the Genesee Laboratory, Batavia, N. Y. and we are indebted to him for the following information: "There was anatomical evidence of a chronic nephritis, hypertrophy of the left ventricle of the heart, a tumor in the posterior part of the pituitary gland with partial destruction of the back of the sella turcica, marked atrophy of the thyroid gland, some hypertrophy of the adrenals, marked atrophy, or better, hypoplasia of the ovaries and uterus."

BALANCE STUDIES

The patient was transferred to the metabolic unit on September 13, 1941, for the purpose of investigating the effect of androgens on her nitrogen, phosphorus, calcium and magnesium balances. These were followed continuously for 230 days, with the exception of three interruptions of two or four days, but never at a time when this interfered with the interpretation of results. She was placed on a basic diet which was thought to be adequate in its caloric content, to contain sufficient vitamins and to provide a liberal intake of protein and calcium. The same menu was eaten each day. Its composition was as follows:

Estimated		Found by Analysis
Protein.....	100 Gm.	97.0 Gm.
Carbohydrate...	154 Gm.	not done
Fat.....	56 Gm.	not done
Calcium.....	1.400 Gm.	1.035 Gm.
Phosphorus.....		1.480 Gm.
Calories.....	1,600 (approximately)	

The intake of nitrogen, calcium, magnesium and phosphorus was determined by the analysis of complete sample diets which were prepared from time to time during the course of the investigation. Since the

analyses exhibited no definite trend, the average values of the four elements mentioned were taken as the true intake in each period. It was possible to hold rigidly to this formula except in two periods, 6 and 11, when the carbohydrate intake was deliberately increased by 150 Gm. each day.

Observations were made over a total of forty-six five-day periods, the first six periods serving as controls. Androgen dosages are shown in Table I and Figures 2, 3 and 4. Certain deviations in dosage may be briefly mentioned at this point: In period 7 the 25 mg. dose of testosterone propionate was started on the second day, accounting for the total dose of only 100 mg. in this period. In period 15 one dose of 50 mg. was given on the first day and 10 mg. on each of the subsequent four days, making the total amount 90 mg. In the case of androsterone the daily dose was 25 mg. for the last four days of period 39 and the first four days of period 40. On the first and last days of this ten-day interval the dose was 12.5 mg.

Analytical Methods. Nitrogen in urine and feces was determined by the macro-Kjeldahl method, with determination of urinary nitrogen on twenty-four-hour specimens. Five-day aliquots of urine were pooled for the calcium, phosphorus and magnesium determinations. Stools were marked in five-day periods by the use of carmine. Calcium and magnesium were determined gravimetrically by the method of Washburn and Shear.³³ Phosphorus analyses were also carried out gravimetrically by the method of Epperson¹⁰ and checked according to the Fiske-Subbarow¹¹ procedure.

RESULTS OF METABOLIC STUDIES

Nitrogen Balance (Table I, Fig. 2). Maximum retention was achieved on an intramuscular dose of 25 mg. of testosterone propionate daily. Lowering the dose from 50 mg. to 10 mg. daily was soon followed by a sharp increase in urinary nitrogen, but the increase did not become great enough at the end of eight days to produce a negative nitrogen balance. Return to the previously high level of nitrogen retention

did not occur when the 10 mg. dose was increased to 20 mg. Raising the dose from 20 to 50 mg. daily was followed again by definite nitrogen retention but at a lower level than had previously been noted with doses of 25 and 50 mg. The authors are not

TABLE I
NITROGEN, CALCIUM, PHOSPHORUS AND MAGNESIUM
BALANCES DURING THERAPY WITH ANDROGENS

Period No.	Nitrogen Balance Gm./Period	Calcium Balance Gm./Period	Phosphorus Balance Gm./Period	Magnesium Balance Gm./Period	Androgen mg./Period	Weight Kg.
1	+0.98	-1.322	-0.482	-0.096	None	53.01
2	-1.12	-1.380	-0.568	-0.119	None	52.87
3	-0.36	-1.402	-0.640	-0.180	None	52.18
4	-0.81	-1.350	-0.601	-0.133	None	52.45
5	-0.45	-1.227	-0.749	-0.089	None	52.35
6*	+6.68	-0.633	+0.537	-0.267	None	52.06
Testosterone propionate						
7	+0.76	-1.315	-0.195	+0.066	100	53.62
8	+10.82	-1.146	+0.105	+0.019	125	53.15
9	+15.31	-0.515	+0.278	+0.052	125	53.55
10	+16.26	-0.533	+0.357	+0.099	125	54.16
11*	+21.98	-0.450	+1.260	+0.013	125	55.21
12	+14.13	-0.385	+0.423	-0.026	125	56.50
13	+16.59	-0.164	+0.486	+0.070	200	56.74
14	+13.89	-0.042	+0.485	-0.112	250	56.78
15	+11.84	-0.281	+0.461	+0.091	90	57.45
16	+3.90	-0.180	-0.213	-0.118	50	57.39
17	+2.13	-1.093	-0.235	+0.042	100	57.38
18	+1.38	-1.106	+0.199	+0.046	100	57.38
19	+2.10	-0.242	+0.270	-0.087	100	58.02
20	+2.19	-0.250	+0.135	-0.062	125	58.11
21	+7.47	+0.248	+0.464	-0.023	250	57.86
22	+9.57	+0.132	+0.508	-0.115	250	57.89
23	+8.38	+0.248	+0.343	-0.144	58.43
24	-4.28	+0.105	-0.554	-0.099	58.42
25	-14.72	-0.088	-1.056	-0.066	57.74
26	-14.30	-0.148	-0.870	-0.021	57.07
27	-10.77	-0.688	-1.097	-0.079	57.40
28	-8.61	-0.716	-0.808	-0.054	56.34
29	-9.14	-0.401	-0.704	0.000	56.00
30	-8.12	-0.433	-0.384	+0.012	55.88
31	-3.80	-0.718	-0.630	-0.018	55.64
32	-5.65	-0.905	-0.760	-0.032	55.48
33	-3.12	-1.245	-0.550	-0.052	55.71
34	-2.08	-1.363	-0.454	-0.034	55.52
35	-3.87	-0.986	-0.650	-0.030	55.71
36	-0.95	-0.943	-0.529	-0.058	55.55
Androsterone						
37	-2.09	-0.825	-0.498	+0.032	62.5	56.09
38	-1.86	-0.850	-0.625	+0.018	62.5	56.11
39	-2.24	-0.980	-0.374	+0.018	112.5	56.26
40	-0.26	-0.953	-0.384	-0.019	112.5	56.09
Dehydroisoandrosterone						
41	-0.13	-0.926	+0.811	-0.017	125	55.77
42	-0.953	-0.722	+0.022	125	56.19
Testosterone propionate						
43	-1.37	-1.083	-0.635	+0.067	125	56.89
44	+7.93	-1.056	-0.055	+0.012	125	56.93
45	+10.53	-0.806	-0.026	-0.041	125	57.25
46	+10.03	-0.855	-0.166	-0.053	125	57.97

* 150 Gm. of added carbohydrate given daily during these periods. Values are derived from actual analysis of diet, urine and feces. Each metabolic period is five days. Body weights recorded are under basal conditions on the first day of each period. Methods of analysis and intake given in text.

sure whether this last result was due to (1) some refractoriness on the part of the patient

toward the hormone which had developed during the earlier administration of the 50 mg. dose or (2) whether she had arrived at a period when so much nitrogen had been retained that a diminishing effect was to be expected. After the hormone had been

such as one might expect in a normal subject. Later (period 11), while the patient was under the full effects of a daily dose of 25 mg. of testosterone propionate intramuscularly, the same amount of extra carbohydrate was given again. It will be

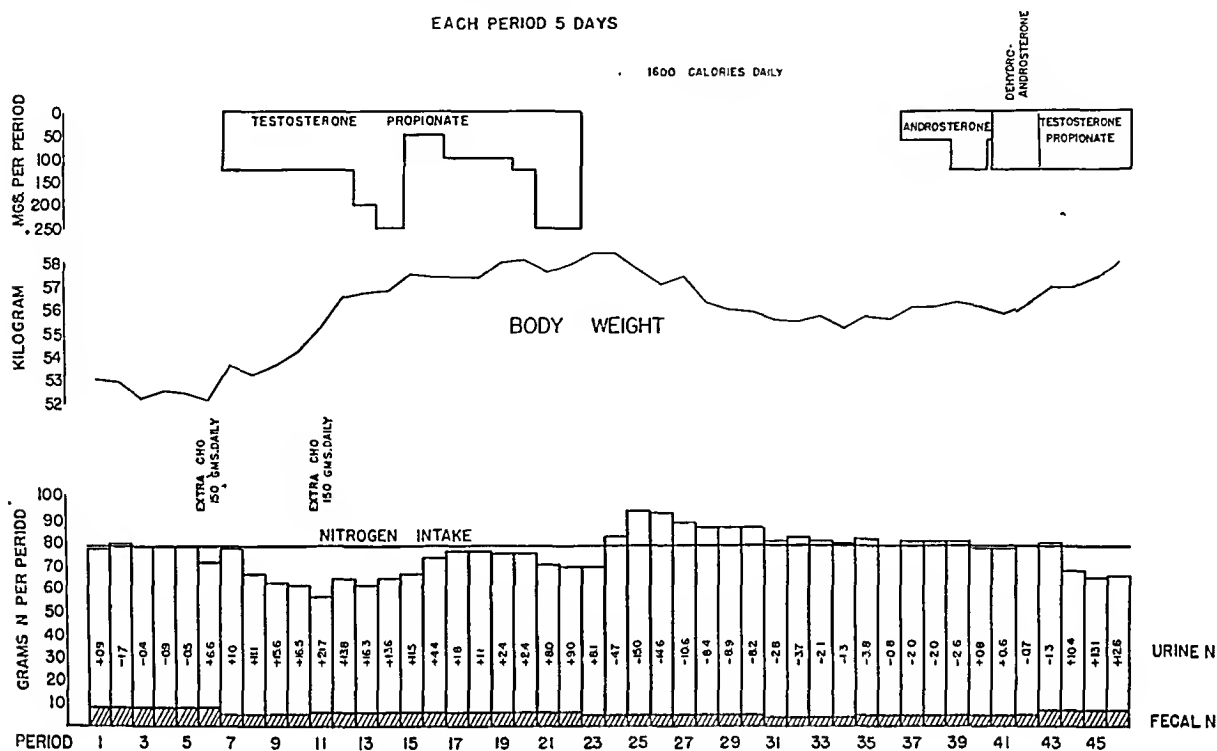


FIG. 2. Nitrogen balance in patient J. D.

discontinued duration of the nitrogen-sparing action of the 50 mg. dose given in period 22 was exactly five days. Loss of previously stored nitrogen continued at a high level for thirty-five days after stopping the hormone and nitrogen equilibrium certainly was not attained even after sixty-five days. Neither androsterone nor dehydroisandrosterone exerted any appreciable nitrogen-sparing effect when given what was believed to be an adequate trial in doses of 25 mg. daily intramuscularly. That the patient was again receptive to the 25 mg. dose of testosterone propionate is shown by her response in periods 43 to 46. An interesting response was noted in periods 6 and 11. In the former period no testosterone propionate had been given. Here the extra calories from carbohydrate had a small but definite nitrogen-sparing effect

observed that the nitrogen-sparing effect of the added carbohydrate was superimposed upon that of the testosterone propionate. The extra sugar produced a mild glycosuria (7 to 8 Gm. per day), some apathy and moderate drowsiness. Net nitrogen retention after eighty days of testosterone propionate therapy was 159 Gm. Net loss of nitrogen during the seventy days in which the hormone was discontinued was 90 Gm. The balance, therefore, revealed a gain of 69 Gm. It appears evident that the initial storage of nitrogen was so great that considerable amounts of it must have been deposited, presumably in the muscles. While the initial loss of nitrogen was fairly rapid upon discontinuing treatment, about 43 per cent was still present in the tissues even after seventy days. The data also suggest that a much smaller dose of testosterone

propionate might suffice to enable a subject to retain nitrogen which had previously been deposited. (Periods 15 to 18.)

Creatine and Creatinine Excretion. During the six control periods the urine contained an average of 520 mg. of creatinine (range

Howard et al.¹⁶ have shown with convalescent fracture patients and Deitrick and Whedon⁷ with healthy normal adults, immobilization in bed may lead to a marked increase of urinary calcium excretion.

The loss was gradually checked by testo-

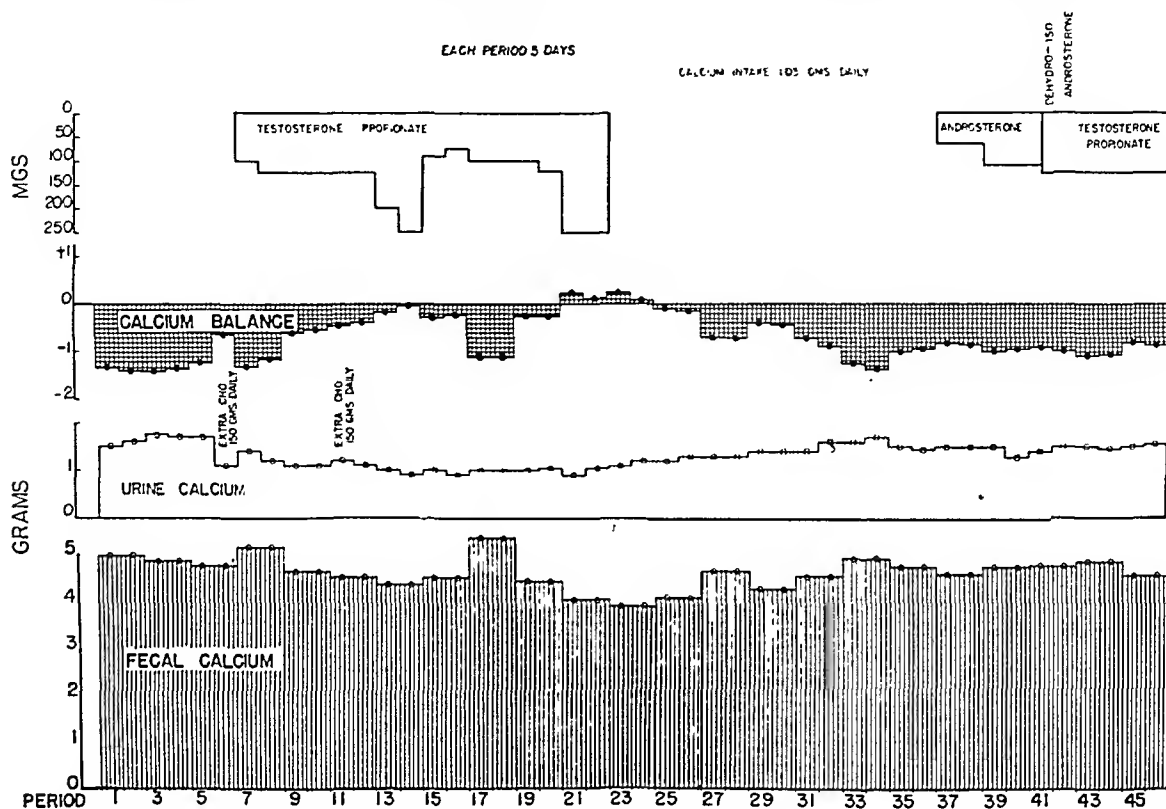


FIG. 3. Calcium balance in patient J. D. Values plotted represent Gm. and mg. per period, respectively. Because of difficulty in separation of stools into periods, the average value of two periods has been used in constructing the curve of excretion of fecal calcium. The high stool calcium in periods 17 and 18 are due to a high value in period 18.

437 to 584 mg.) and 720 mg. of creatine (range 630 to 810 mg.) daily. With the administration of testosterone propionate, the creatinine gradually increased to around 770 mg. daily. The creatine, however, did not decrease as it has in other individuals studied.³⁷ Nevertheless, when the injections were discontinued, the usual increase of creatinuria took place, amounting to over 1 gm. daily from the twentieth to the thirtieth days.

Calcium Balance (Table 1 and Fig. 3). Calcium loss from the skeleton was definite during the control periods. Unfortunately, it was necessary to keep the patient in bed because of her back pain; hence the negative balance was probably aggravated. As

sterone propionate. During treatment the urinary calcium excretion diminished, and to a slight but definite degree fecal calcium was likewise decreased although no net retention of calcium was observed. A sudden increase of fecal calcium in period 18 is difficult to explain. The value obtained on analysis was higher than any during the entire investigation and may have been in error.

In period 6 when extra carbohydrate was given there was diminution of urinary calcium almost as great as the change with testosterone propionate. Hence the nitrogen-sparing effect previously discussed seems to have been accompanied by saving of calcium and, as will be seen later, phosphorus

as well. Furthermore, one may question whether the negative balance of calcium was exaggerated by an insufficient caloric intake. By the usual standard her dietary calories were presumed adequate in that she maintained her weight as well as a

of the theoretical phosphorus balance. As shown by Reifstein *et al.*²⁶ it is possible to calculate a theoretical phosphorus balance if one knows the calcium and nitrogen balances, assuming that the calcium-phosphorus ratio of bone is 2.23 and the nitrogen-

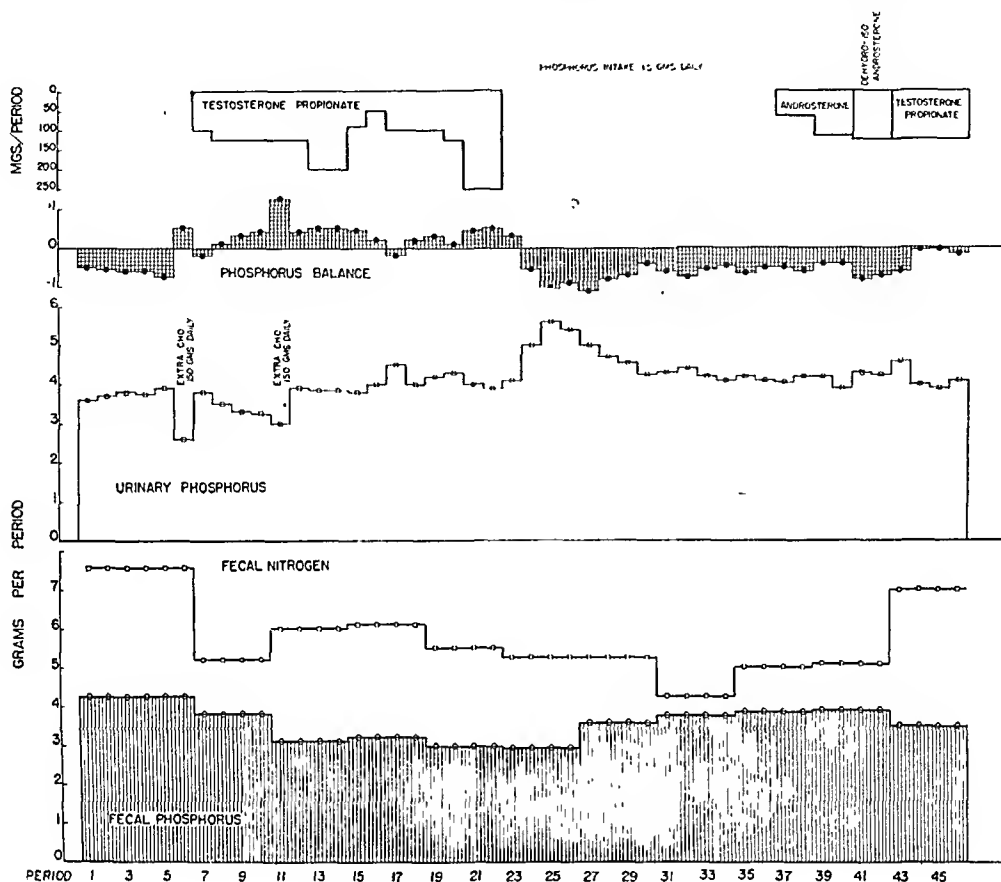


FIG. 4. Phosphorus balance on patient J. D.

fairly constant nitrogen equilibrium during the control periods.

Phosphorus Balance (Table 1, Fig. 4). Phosphorus excretion in the urine was not affected, but fecal phosphorus decreased in the periods of nitrogen retention and small net retentions of phosphorus were observed. After testosterone propionate was discontinued there was a sharp increase in urinary phosphorus with a gradual return of fecal phosphorus to higher levels. The depressant effect of extra carbohydrate on urinary phosphorus, as shown in period 6, appeared similar to the results obtained on nitrogen and calcium excretion.

The net retention of phosphorus was significant when checked by the calculation

phosphorus ratio of muscle is approximately 15. For example, during periods 7 to 22 when the patient was under testosterone propionate therapy, she retained 150.3 Gm. of nitrogen and lost 7.4 Gm. of calcium. Observed phosphorus retention was 4.8 Gm. To this must be added 3.3 Gm. of phosphorus which was made available from the calcium loss, making a total of 8.1 Gm. of phosphorus. The theoretical phosphorus retention, on the basis of 150 Gm. of nitrogen retained, is 10 Gm. so that the observed balance of phosphorus is in fair agreement with the theoretical.

Magnesium Balance (Table 1). Small amounts of magnesium were retained during periods of testosterone propionate ther-

apy mainly because of diminished fecal excretion of this substance.

Energy Metabolism. During the patient's residence in the metabolism unit periodic estimations were made of her basal metabolic rate, respiratory quotients and

TABLE II
ENERGY METABOLISM IN CUSHING'S SYNDROME

Period No.	Date	Testosterone Propionate, Total Additive Dose mg.	Basal Respiratory Quotient	Basal Calories /M ² /Hr.	Basal Metabolism (Aub-Dubois)* %
3	10/24/41	0	0.765	25.3	-38.0
4	11/1/41	0	0.762	28.0	-31.5
5	11/7/41	0	0.775	26.9	-33.3
9	12/3/41	250	0.739	32.4	-20.5
11	12/16/41	575	0.801	32.6	-19.5
(High carbohydrate diet—period No. 11)					
14	12/27/41	950	0.764	30.9	-22.5
16	1/8/42	1270	0.759	31.3	-23.0
20	1/30/42	1715	0.755	26.0	-33.0
25	2/25/42	2340	0.750	30.9	-23.0
34	4/10/42	None for 55 days	0.794	26.0	-33.0

* Determination of basal metabolic rate was carried out by use of the Tissot spirometer with subsequent gas analyses after the method of Haldane.

ability to utilize glucose. These observations were always begun fourteen hours after the previous evening meal. Expired air was collected in a Tissot spirometer for periods of ten minutes or more and analyses for oxygen and carbon dioxide were made with the Haldane apparatus.⁸

When glucose was given, the dose unless otherwise specified was 25 Gm. so that oral and intravenous administration could be compared. Sugar in the blood was determined by the method of Benedict,²⁵ that in the urine by the method of Hawkins and Van Slyke.²⁵

Basal Metabolism. The consistently low basal metabolic rate was undoubtedly an expression of the deficient protein content of the body tissues. It will be noted (Table II) that a rise in the basal metabolic rate occurred during the intensive testosterone propionate therapy. Control levels were on

the average minus 34 per cent while during treatment the rate rose to minus 21 per cent. In period 20, while the patient was still taking testosterone propionate, there appeared to be a fall to the pretreatment level. Whether this was due to a technical error could not be determined; on the other hand, similar fluctuations in basal metabolic rates under androgen therapy have been observed by others. Howard, Wilkins and Fleischman¹⁷ treated sexually immature dwarfs with methyl testosterone and noted irregular, unexplained fluctuations in the basal metabolic rate. These were thought *not* to be due to the influence of the thyroid gland since the same results were obtained upon treating a cretin. Under hormone therapy our patient's blood cholesterol fell from over 260 mg. per cent in the control period to an average of 160 to 170 mg. per cent in period 16. By period 29 it had risen again to 280 mg. per cent.

Conclusions drawn from respiratory quotients are extremely hazardous when the data are obtained from individuals whose tissues deviate so far from the normal as in this patient. Aside from the fundamental disturbances in the handling of foodstuffs which we were trying to explore there was superimposed the condition of protein deficiency.

The basal respiratory quotients (Table II), were uniformly low²⁷ in spite of her slightly increased protein intake (about 1.8 Gm./Kg.). Even in period 11 when 150 Gm. of extra carbohydrate were given daily, the basal respiratory quotient was 0.801. Wells and Kendall,³⁴ Long²¹ and Ingle and Thorn¹⁸ thought the "sugar hormones" in some way interfere with carbohydrate oxidation. Thorn and co-workers³¹ found that the respiratory quotient of some patients with Addison's disease was high and treatment with "sugar hormones" diminished these high values. The low respiratory quotient values of our patient, therefore, might be partially explained on the basis of defective carbohydrate oxidation. The finding that in acute experiments she was able to raise her respiratory quotient signifi-

cantly and oxidize considerable amounts of carbohydrate casts doubt on such a possibility.

Sugar Tolerance.—Oral and intravenous sugar tolerance tests were done before and during testosterone therapy. While all the

The respiratory quotient increased significantly after each dose of glucose (Fig. 5), indicating that considerable amounts of carbohydrate were being oxidized. This is shown more clearly in an experiment done 55 days after testosterone propionate ther-

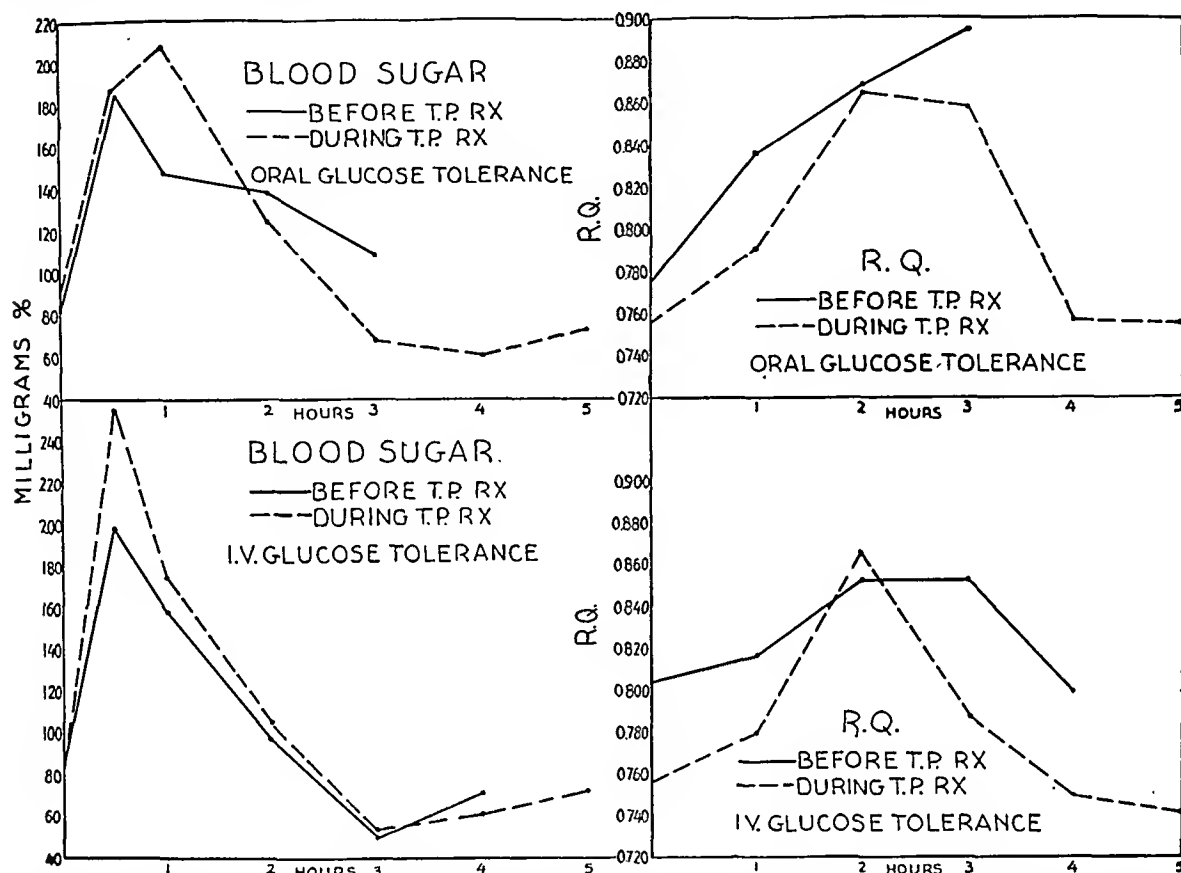


FIG. 5. Oral and intravenous glucose tolerance and respiratory quotients obtained before and during testosterone propionate therapy. T.P. = testosterone propionate; Rx = therapy.

tests were not carried out for a uniform length of time, certain conclusions may be drawn from Figure 5. During the control periods the oral test showed a diabetic type of curve while during treatment with testosterone propionate the blood sugar level dropped more rapidly, being below control values by the third hour. Since the response to intravenous injection before and after treatment was practically the same, the insulin mechanism was probably not affected but improved absorption of glucose from the gastrointestinal tract is suggested.*

* Freeman, Looney and Hoskins¹³ found marked variation in glucose tolerance curves when duplicate deter-

apy had been discontinued. (Table III.) In this experiment following the injection of glucose the non-protein respiratory quotient rose to 0.938. From the information in this table an estimate of the carbohydrate oxidized can be made but the amount deposited in liver and muscles is, of course, unknown. Of the 27.5 Gm. of glucose injected 9.5 Gm. were recovered from the urine. In the five hours she produced 89.4 calories from carbohydrate, i.e., 21.8 Gm. of glucose were oxidized. In other words, 3.8 Gm. over and above the glucose given were accounted for. Although it appears

minations were made in normal individuals. However, the subjects were not on a constant diet.

that during the first hour after glucose both protein and fat were being spared, if one takes an average of the first two hours little if any protein appeared to have been spared by the carbohydrate but the oxidation of fat was decreased.

TABLE III

FIVE-HOUR CARBOHYDRATE BALANCE STUDY FOLLOWING INJECTION OF 0.5 GM. GLUCOSE/KG. OF BODY WEIGHT IN CASE OF CUSHING'S SYNDROME*

Time Hours	Urine N†	Urine Sugar	Blood Sugar	Non-protein R.Q.	Total Calories Derived from		
					Protein	Fat	CHO
	Gm	Gm	Mg %				
Fasting	0.278	0	55	0.783	7.4	22.8	8.1
½	191				
1	0.216	6.3	105	0.885	5.7	13.2	23.8
2	0.394	3.2	62	0.938	10.5	6.0	25.2
3	0.355	...	56	0.893	9.4	10.3	18.9
4	0.291	0	...	0.789	7.7	24.2	10.3
5	0.253	0	66	0.799	6.7	22.5	11.2

* 27.5 Gm. of glucose injected during thirty minutes.

† Urine was obtained at hourly intervals by means of an indwelling catheter. Blood sugar was obtained immediately after the urine specimen on the average of fifteen minutes following release of the catheter clamp. (Following withdrawal of each urine specimen, the bladder was washed with sterile distilled water.)

After the patient had been on the low caloric rice diet of Kempner²⁰ for three months an oral glucose tolerance test gave the following results: Fasting blood sugar 65 mg. per cent, one-half hour after glucose 87 mg. per cent, one hour 92 mg. per cent and two hours 84 mg. per cent. This in no way resembled the former or subsequent diabetic type of curves. The change must have been due to the low caloric, high carbohydrate, low protein diet. It appears likely that either glycogen stores had been depleted or glycconeogenesis had decreased.

Neutral 17-ketosteroid Assays. Determinations of neutral 17-ketosteroid excretion were carried out for the first twenty-five periods in 1941 according to the method of Holtorff and Koch.¹⁵ Control values averaged 19.1 mg. per twenty-four hours while under testosterone propionate therapy the patient excreted an average of 32 mg. per twenty-four hours. Since testosterone propionate is converted to and excreted as a

17-ketosteroid, the rise in androgen output under treatment was to be expected. Three and one-half years later further determinations were made when she was placed on the 1,000 calory rice and raisin reduction diet. The 17-ketosteroid values as determined by the modification of Talbot et al.²⁹ fell from a control level of about 30 mg. per day while she was on an average hospital diet to an average of 20 mg. per day after she had been on the low protein diet for over a month. The higher level of excretion during the control days of this time may have been due to the different method but more probably was associated with increased severity of the disease. The diminished excretion of androgen while she was on the diet was probably related to its extremely low protein content. Attempts to suppress adrenal function further with desoxycorticosterone acetate²⁸ were made at this time. Gradually increasing doses of 0.5 mg. to 2 mg. were given daily over a period of forty days. As feared the blood pressure increased and headaches were worse so that treatment was discontinued. No further reduction of neutral 17-ketosteroid excretion was observed. Substitution of progesterone²³ likewise had no effect.

COMMENTS

The hyperadrenocorticism in our patient was unquestionably due to basophilic hyperpituitarism with excessive production of adrenocorticotrophic hormone as originally postulated by Cushing.⁵ It is unfortunate that roentgenologic evidence for this was not found until shortly before her death. Evidence of diminished pituitary activity as it is related to the gonads was revealed by amenorrhea and markedly decreased or even absent gonadotrophic hormone in the urine. The latter has also been reported by Albright¹ and Jores.¹⁹

It is the impression of the authors that in many respects the condition of this patient was improved to a considerable degree by treatment with testosterone propionate. Her general strength and well being were

greatly improved, and her mental outlook and spirits were better. She was up and about without too many complaints, was able to return to school, ride her bicycle and play outdoors; whereas before treatment her backache and abdominal pains were so severe that she was compelled to lie in bed most of the time and, indeed, for a period required immobilization on a Bradford frame. Surprisingly little masculinization was encountered despite the enormous amount of male hormone she received.

From the laboratory point of view nitrogen and phosphorus retention and diminished excretion of calcium were demonstrated. These confirm the observations of Albright et al.¹ Another beneficial effect may have been a more normal type of sugar tolerance curve.

In other respects the condition of our patient deteriorated even while under treatment. The hypertension became more severe, retinal arteriosclerosis increased, headaches were intensified and she developed auricular fibrillation. It is possible that the androgen contributed somewhat to these effects because of its electrolyte-retaining properties.

After intensive therapy was relaxed the unfavorable conditions which developed were related mainly to the osteoporosis, polycythemia, cardiovascular system and the kidneys. While it is possible that superimposed infection of the urinary tract hastened the onset of uremia, we believe that the intense vascular changes were responsible primarily for the gradual decrease of renal function and final uremic state.

Of more than passing interest was the temporary improvement which took place on the low caloric rice diet of Kempner²⁰ and which was accompanied by loss of weight, decrease of blood pressure, observation of a normal sugar tolerance curve and decrease of neutral urinary 17-ketosteroids. The latter decrease suggests lowered formation of certain steroids as a result of decreased precursors in the diet, and it is unfortunate that we were not able to obtain

information on the excretion of urinary corticoids at this time.

The sudden appearance of generalized muscular weakness, fainting spells and decrease of serum proteins suggests that the depletion of protein from the tissues had been seriously aggravated by the diet. One wonders whether this could have been prevented by the simultaneous administration of testosterone propionate. Such a combination of therapeutic measures deserves a trial although the possibility of spontaneous remissions must be borne in mind.^{3,5,30}

SUMMARY

Clinical and metabolic observations are presented in a case of Cushing's syndrome studied continuously for 485 days and followed closely for five and one-half years.

Treatment with testosterone propionate* intramuscularly produced the following effects:

1. Retention of nitrogen. The maximum effect was achieved with 25 mg. daily. The data also suggest that a much smaller dose of androgen might suffice to hold in the body nitrogen which had previously been deposited at a high level of dosage. When added carbohydrate was given, its nitrogen-sparing effect was superimposed on the effect of the testosterone propionate. Seventy days after treatment had been discontinued over 40 per cent of the deposited nitrogen was still retained by the body.

2. Retention of phosphorus.

3. Diminished calcium loss from the body.

4. Retention of magnesium.

5. A rise of the basal metabolic rate toward but not to the normal level.

6. Possibly better absorption of glucose from the gastrointestinal tract with resulting improved sugar tolerance.

7. Clinically, there was improvement of those symptoms associated with calcium loss

* The endocrine products used in these studies were furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

from the skeleton and with protein depletion of tissues (osteoporosis, pain, strength, "well being"). Symptoms and signs relating to the vascular system were not improved but progressed while under treatment.

The patient was able to oxidize considerable amounts of carbohydrate. The implications of this with regard to the theory that the "sugar hormones" oppose peripheral oxidation of carbohydrate is discussed.

For a brief period she improved while on a low protein, low caloric, low salt diet. After several months this produced severe weakness.

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Insulin Mixtures and Conservation of Insulin*

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MY colleagues and I have had almost ten years of experience with insulin mixtures, starting shortly after Lawrence and Archer¹ and Graham² had announced that they were finding mixtures helpful. Our early results were not entirely satisfying, but procedure for adjusting dosages has improved over the years and we now are obtaining reasonable control of glycosuria with only one injection daily in a fair majority of cases of what we call grade 4 diabetes, that is, cases in which the diabetes is of such severity that the total daily insulin requirement of the patient exceeds 30 units.³⁻⁷

We have not used mixtures prepared by the manufacturer. Failure to do so is because of uncertainty regarding the stability of such preparations.⁸ Also we have not attempted the preparation of mixtures in the insulin vial although this has been proposed by some physicians. Instead we have instructed our assistants and patients to make the mixture in the syringe according to the technic herein described. The procedure has the disadvantage of being somewhat difficult to teach to patients and for that reason it is unsuitable for the very ignorant or for those who are handicapped by poor vision. For such individuals we resort to other methods of insulin administration. In most cases, however, the patient has been able to acquire the technic of making mixtures and the advantages of the procedure are important. They are: (1) that in a large proportion of all cases adequate control of glycosuria is obtainable with a single injection daily; (2) that continued insulin action is assured over the night with little danger of reaction in the night and (3) that the total daily unitage of insulin required is usually somewhat smaller than

the unitage necessary for comparable control of glycosuria when dependence must be placed either on soluble insulin or on protamine zinc insulin used alone.

Another very great advantage of insulin mixtures prepared in the syringe is that, being tailor-made, each component of the mixture can be adjusted to fit the needs of the individual. Requirements differ with different patients. Some need a mixture with more quick action; others one with more retarded action. Also in our experience the requirements of the individual are likely to change from time to time. By using mixtures the amount of each type of insulin can be fitted to the individual and later can be altered to meet his changing requirement. In the majority of cases, two parts of soluble insulin added to one part of protamine zinc insulin best fits the needs most of the time. This is a ratio of 2 of soluble insulin to 1 of protamine zinc insulin. In other cases other ratios have been advantageous. The appropriate ratio rarely exceeds 3:1 or falls below 1:1. A ratio lower than 1:1 usually implies that protamine zinc insulin alone will do all that is required. As was shown by Colwell and his colleagues^{9,10} when the ratio is less than 1:1, the amount of regular insulin contained in the mixture is largely bound by the excess of protamine present in the protamine zinc insulin. It thereby is converted into insulin with retarded action. The action of an insulin mixture in which the ratio exceeds 1:1 is intermediate between the quick action of soluble insulin and the retarded action of protamine zinc insulin. The action of such mixtures may be monophasic as Colwell has maintained; nevertheless, some rapid action provides for the elevated insulin requirement provoked

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by the taking of food during the day and enough slow or retarded action persists to provide for the diminished but continuing requirement for insulin in the fasting hours of the night.

Protamine insulin was developed by Hagedorn and his colleagues¹¹ between 1934 and 1935. Its stabilization and additional prolongation of action by addition of zinc soon followed, and protamine zinc insulin became available commercially in January, 1937. The action of this product was sufficiently prolonged to permit control of diabetes over the night when only one injection was given the preceding morning. It also provided for some overlap from one twenty-four hour period to the next, an insulin insurance from one day to the next as Joslin¹² aptly termed it.

The characteristics of the new insulin gave rise to the hope that its use alone would permit control of glycosuria with only one injection daily, but this hope soon had to be abandoned. In cases of mild diabetes, that is, cases in which a total daily dose of not more than 20 units is required, the condition can be handled safely by the use of only protamine zinc insulin, but in cases of severe diabetes a dose sufficient to prevent gross glycosuria after meals commonly precipitates an insulin reaction in the night. Night is a bad time for a reaction because the patient and his family are asleep. Furthermore, the hypoglycemia which develops from an overdose of protamine zinc insulin comes on so gradually as to be almost symptomless, and the patient may remain quite unaware that his blood sugar has fallen to unphysiologic levels. This may go on unrecognized for weeks or months or even for years. The problem may be further complicated in some patients by what Bowcock¹³ called "paradoxical glycosuria." In these instances, without symptoms being provoked, the blood sugar according to Bowcock's hypothesis, when it reaches certain low levels, trips the mechanism which releases sugar from the liver and the amount of sugar thus released exceeds what can be utilized immediately. Glycosuria then occurs and the patient in

consequence is led to increase still more the already excessive dose of insulin until finally he is taking a sufficient unitage to precipitate a dangerous reaction.

An extreme example of postponement of ill effects of unappreciated overdosage with protamine zinc insulin came to my attention very recently. The patient, a man forty years of age, had been using protamine zinc insulin for ten years, taking a single dose daily. He had noted no ill effects although the occasional appearance of sugar in his urine had led him to gradual increase of his dosage until for several years he had taken 100 units every day. Then suddenly and without much warning he suffered from a severe convulsion with loss of consciousness and hemiplegia. Fortunately the hemiplegia was transitory. In other instances permanent cerebral damage has resulted from such overdoses.

In the case which I have mentioned the patient apparently was able to tolerate an excessive dose of insulin for many years. This is unusual. As a rule vague but unpleasant symptoms develop fairly early even when the patient experiences none of the symptoms which commonly are attributed to insulin reaction, symptoms such as sweating, anxiety, tremor and diplopia, with later loss of consciousness and convulsions. A fair proportion of diabetic patients who come to the Mayo Clinic using protamine zinc insulin complain on arrival of headaches, backaches and leg aches, associated with feelings of exhaustion and weakness with an incapacity for mental concentration; their symptoms disappear soon after the dose of insulin has been lowered. In a few instances actual mental deterioration has been evident and then recovery has been delayed.

The symptoms mentioned also are observed in patients who use mixtures of soluble and protamine zinc insulin, especially when the amount of protamine zinc insulin is large. Therefore, when the total insulin requirement is large, involving the use of more than 20 units of protamine zinc insulin combined with 40 units of soluble insulin, we now advise either increasing

only the amount of soluble insulin in the mixture or abandoning the attempt to obtain control of glycosuria with a single injection daily and giving a supplementary dose of soluble insulin before the evening meal.

Control of glycosuria in some instances is less satisfactory with mixed insulins than we should like to have it. In certain cases results superior to those obtainable with mixed insulins are to be had with injections of soluble insulin given three or four times daily or with protamine zinc insulin and soluble insulin administered in separate sites. In a very few cases of severe diabetes best control has resulted from giving soluble insulin before breakfast and globin insulin before the midday meal. The action of globin insulin seems not to extend much beyond the sixteenth hour. However, with two injections a day, one of soluble and one of globin insulin, this difficulty is overcome. We have had relatively little experience with globin insulin and none with histone insulin. The latter is made with protamine obtained from the thymus and, like protamine insulin, is turbid. Bailey and Marble¹⁴ showed that its action parallels closely that of protamine zinc insulin although its activity is slightly less prolonged.

DIRECTIONS FOR USE OF INSULIN MIXTURES

Filling the Syringe. As Sprague^{6,7} has emphasized use of extemporaneous mixtures of protamine zinc insulin and soluble insulin in one syringe calls for precaution to prevent introduction of one kind of insulin into the other vial. An appropriate volume of air is first injected into the vial of protamine zinc insulin and the needle is withdrawn without any insulin being permitted to enter the syringe. Then the desired dose of soluble insulin is drawn into the syringe in the usual manner. After this the needle is again inserted into the vial of protamine zinc insulin, and the desired dose is allowed to flow into the syringe and to overlies the soluble insulin which is there already. The two insulins are then mixed by drawing a small bubble of air into the syringe, inverting the syringe several times and then expelling the bubble.

Adjusting the Dose of Insulin. By adjustment of the size of each component of the insulin mixture more or less of either slow or quick insulin action is obtainable. This adjustment cannot be rigidly prescribed although usually some variation of the plan outlined in subsequent paragraphs proves satisfactory.

Two urine tests a day are necessary, one before the morning meal, the other before the evening meal. The urine should be freshly secreted; that is, the bladder should be emptied approximately thirty minutes before collection of the specimen for examination. In the early treatment of a patient tests are made four times daily; that is, before each of the three principal meals and at bedtime. Later two, three or four tests daily are secured, depending on the severity of the diabetes and the desired precision of control. Usually with diabetes of moderate severity adequate information is obtainable by testing twice daily, before breakfast and before supper.

Sugar in the urine before the morning meal calls for more protamine zinc insulin (more late action) whereas sugar in the urine before the evening meal demands more soluble insulin (more early action).

When a change is to be made from use, either of protamine zinc insulin alone or of multiple doses of soluble insulin, a safe initial dose of the mixture is two-thirds of the total daily units taken recently. The ratio at the start is 2:1; that is, 2 units of soluble insulin for each unit of protamine zinc insulin. However, if the patient has been using a very large unitage of protamine zinc insulin, something less than two-thirds of the recent dosage is desirable because of the holdover of the effect of the large preceding dose of protamine zinc insulin. For example, if a patient has been taking 60 units of protamine zinc insulin, I should give no insulin at all for twenty-four hours and then begin with approximately two-thirds of 60, which would be approximately 40 units of a mixture with a 2:1 ratio; for example, 28 units of soluble and 14 units of protamine zinc insulin. Rarely should the initial dose exceed 60 units, and

in the absence of evident acidosis increases of dosage should be made cautiously during the first few days of treatment. The full effects of the starting dose may not be apparent for several days.

Later adjustments are made as follows:

When the test of the morning urine has been grade III or IV* for three or four mornings in succession the protamine zinc insulin compound of the mixture is increased by 2, perhaps by 4 units. However, if this necessitates giving more than 20 units of protamine zinc insulin, the attempt is made to obtain control by increasing the soluble insulin component of the mixture; and if this provokes an insulin reaction during the day, by giving instead a small dose of soluble insulin before the evening meal. Likewise, when the test of the morning urine has been 0 for several successive days, usually not more than three, the protamine zinc insulin component is reduced in size by 2, perhaps 4 units. For traces of sugar in the morning urine (tests grade I or II) no change is made. The presence of a trace of sugar in the morning provides a measure of assurance that the dose of protamine zinc insulin has not been excessive.

When the test of the urine before the evening meal has been grade III or IV for two or at most three successive days, the soluble insulin component of the mixture is increased by from 2 to perhaps 4 units. This change is made on the following morning. Likewise, when the test of the urine before the evening meal has been 0 for two or more successive days, the soluble insulin component is reduced by 2 or perhaps 4 units.

In most cases when reasonable control of glycosuria has been effected, it is inadvisable to make changes in the doses of the two kinds of insulin more frequently than has been suggested. Factors other than insulin, notably emotional disturbances and variations of food intake, may be responsible for transient glycosuria. On the other hand, the occurrence of a *bona fide* insulin reaction

usually calls for lowering the next day's dose of insulin. When the reaction has developed between breakfast and supper, the soluble component of the mixture should be lowered the following morning. If it has developed in the night, the protamine zinc insulin component should be lowered. The magnitude of the changes made in the insulin dosage depends, as a rule, on the size of the total daily unitage of insulin. When this is less than 40 units, changes in steps of only 2 units are advisable. When it is more than 40 units, changes in steps of 4 units are desirable. Some patients, particularly children, are so sensitive to small changes that alterations of 2 units at a time are sufficient irrespective of the size of the total daily dosage.

Use of Insulin in Emergencies. A single morning dose of insulin, even a mixture of insulins, will rarely provide adequate control of diabetes in emergencies. Many infectious diseases intensify the diabetic state. They seem to provoke a degree of insulin resistance so that larger and more frequently administered doses of insulin are required. Likewise, after serious injuries, especially those involving fractures of the bones, and after operations additional insulin is usually required.

Considerable advantage attends continued use of some protamine zinc insulin in emergencies. Although multiple injections of soluble insulin are also made, prolonged action of the protamine zinc insulin is helpful to insure a continuous insulin effect day and night. When the patient has been maintained either with one injection daily of protamine zinc insulin alone or with a mixture of soluble insulin and protamine zinc insulin, the dose of protamine zinc insulin or that of the mixture is continued as before, with additional injections of soluble insulin made at intervals. Freshly secreted urine is tested for sugar every three hours. It also is tested for diacetic acid whenever the test for sugar is grade IV. For a grade IV test 10 units of soluble insulin is administered. With young children, 6 units may suffice. However, if the test for diacetic acid is positive in a

* The grade IV test with Benedict's qualitative solution is represented by red, grade III by yellow, grades I and II by green turbidities. Essentially the same colored turbidities are obtained with the clintest.

urine that tests grade IV for sugar, adults are given 12 or more units of soluble insulin and children 8 or more units.

With protamine zinc insulin given in the morning, it may not be necessary to test the urine or to administer additional soluble insulin between 10 P.M. and 6 A.M. The severity of the condition determines this. When the emergency has passed and convalescence has begun, the requirement for insulin may decline rather quickly and the supplementary doses of insulin must be diminished. When recovery is complete, the dose of insulin that was effective before the emergency will usually again suffice.

CONSERVATION OF INSULIN

I should like to emphasize a point already made: that use of insulin mixtures properly adjusted has frequently effected a saving of insulin, in that the unitage required for reasonable control of glycosuria has been less in many cases than what had previously been employed. I also wish to emphasize that great saving in the use of insulin can be accomplished by not using insulin at all, except in periods of emergency, with diabetic patients who are grossly overweight. The treatment of choice for the obese diabetic patient is a reducing diet, not insulin. When such a patient is given a diet as low or lower in calories than his basal caloric needs, he usually becomes aglycosuric without insulin and the giving of insulin may only stimulate his appetite and add to his desire to eat beyond his diet. Also when the body weight of such a patient has been lowered to the standard weight for height, a maintenance diet usually can be tolerated without insulin.

When I add the saving of insulin effected by these two means, the resulting conservation of insulin in regard to our patients is impressive. Thus, among one hundred consecutive new diabetic patients using insulin on arrival and treated as ambulatory in the Mayo Clinic, sixteen were obese. These sixteen overweight people had been using a total of 307 units of insulin daily and on their dismissal were using only 80 units. The remaining patients, numbering

eighty-four, had been consuming a total of 2,636 units of insulin every day and on dismissal had lowered their daily consumption to 1,843 units. The total daily unitage for the one hundred patients was 2,943 before arrival and 1,923 on dismissal. This represents an average saving for each patient of about 10 units daily, and a total annual conservation of 372,300 units, or almost one thousand vials of U-40 insulin every year. However, more important is the fact that this conservation of insulin was accompanied by improvement in control of the patients' diabetes.

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A Liberal Regimen of Treatment of Diabetes

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IN the preinsulin era regulation of the diet was the only means of treating the patient with diabetes. The intake of food always had to be reduced; the amount of deprivation depended on the individual patient's supply of endogenous insulin. This meant considerable hardship for the severe diabetic but there was nothing else to be done. The patient was subjected to a rigid course of dietary instruction which he had to follow if he wished to survive.

With the coming of insulin, diets for diabetics gradually became more liberal and eventually were virtually normal. The insulin dosage was adjusted to a particular diet so that the patient's blood sugar level throughout the day was reasonably controlled. Diets used by different physicians varied considerably, from the low and moderate caloric diets to relatively high caloric diets; from low carbohydrate intake to a very high—sometimes unreasonably high—carbohydrate intake. We learned as time went on that generally a patient on a diet with 200 Gm. of carbohydrate and a reasonable caloric intake got along better than one taking only 100 Gm. of carbohydrate and the same number of calories. This fact was of value to the physician and of inestimable comfort to the patient to whom it meant that "life was again worth living."

Looking backward we can see that many queer things were done during this period. For instance, the diet was divided into three equal parts for each of the meals. The average individual ordinarily does not eat that way. Many people are accustomed to taking a breakfast consisting of half a grapefruit, toast and coffee. Suddenly if they become diabetic they had to eat a big breakfast because it was prescribed while they were in the hospital. Some acquired

the habit of eating a big breakfast and learned to like it. Others did not enjoy it and never could adjust to this change in their life routine and gradually returned to their old habits.

Was this drastic change in a patient's dietary habits necessary? I never could see any sense to it. If a patient received 20-10-20 units of insulin a day with a heavy breakfast, the dosage could be changed to 10-10-20 if, with a light breakfast, the patient had a reaction during the morning. Now when a patient takes only protamine zinc insulin in the morning, it is even more essential that he eat a light breakfast for PZI does not begin to work until about noon. Hence during the morning the patient is unprotected and by noon the blood sugar may rise considerably. To prevent this post-breakfast rise when a patient takes a heavy breakfast some insulin is given with the PZI in the morning dose in the same syringe and all in one injection. The amount of insulin necessary can be adjusted quite closely after a few blood sugar checks are done at noon.

The point I wish to emphasize is that experience has taught us that forcing a diabetic patient into an artificial and distasteful routine is like trying to fit a square peg into a round hole and it is not a sensible procedure. The more closely we adhere to his normal living habits the easier the routine is for the patient and the better his cooperation.

Beside this an adverse psychologic factor is introduced by the very word "diet." Question any normal individual, examine him, discover about how much food he has been consuming daily for the past ten years (most people eat much the same from day to day unless they are obese) and then say: "My dear man, I will have to put you on a

diet now which you will have to follow closely." The estimate of what he has been eating for the past ten years will be, let us say, 2,000 calories a day. Now the diet is outlined, these things for breakfast, these for lunch and these for dinner. In doing this let us suppose that instead of giving him a 2,000 calory diet he receives 3,000 calories, that is, 50 per cent more than he has been taking. From the day he starts on the diet, even though it is 50 per cent more food, he will feel starved and that he is being deprived. He is not being deprived of food at all but only of his freedom to choose his food. This tremendous psychologic factor has not received the consideration it deserves in the treatment of diabetic patients.

The importance of this psychologic factor was well brought out during the war when thirty-six conscientious objectors volunteered as guinea pigs for experiments in human starvation at the University of Minnesota Laboratory of Physiological Hygiene.¹ These volunteers were prepared for semistarvation by three months of good eating, with an average of 3,492 calories daily. Then for six months they received two carefully rationed meals a day, totaling 1,570 calories. A daily sample was: pancakes, syrup, apple saucc, cornbread and jam in the morning; potato soup, stew and potatoes in the evening. Their psychologic reactions were most interesting. Although they knew that nobody would try to shove them aside, the hungry men began taking great care to guard their places on the chow line. They showed a strongly possessive attitude toward their food; at the table some leaned suspiciously over their trays "protecting" their rations with their arms. These men were "cultured and refined," the researcuers reported, but soon they all unashamedly licked their dishes. (I have observed the same behavior in diabetic children who were on relatively high diets.) As they became more and more hungry food became the chief subject of their conversation and of their day-dreams. They became fond of poring over cook books and hotel menus. (Diabetics show the same

tendency.) Some of the men started to re-plan their lives and talked of becoming cooks or farmers. They grew increasingly irritable and joked less and less. Eventually they grew too apathetic to bother with shaving, brushing their teeth or combing their hair. Their interest in study gradually collapsed but they felt closely identified with their group and with the starving throughout the world. They occasionally had "spells of elation, sometimes bordering on ecstacy," or were unduly depressed and discouraged. After six months of hunger they required six months to return to normal. During the first three months of rehabilitation their bad table manners and study habits showed little improvement; some men actually became more depressed and irritable than during semistarvation. As the effects of starvation wore off each man lost his sense of close identity with the group and began worrying about his own personal plans for a normal future.

Such a study as this is most revealing and presents food for thought in its relation to the treatment of diabetes. In managing diabetics we do not give diets as low as 1,570 calories but of 1,800 calories or more. However, it must be remembered that even on a 2,000 calory diet, a "planned diet," if the patient's diabetes is not well controlled he is not utilizing all the food and may be losing as much as 240 to 400 calories which are excreted as sugar in the urine. Such a patient, therefore, is actually starved. And even if he is losing but 80 to 100 calories in this manner, which is quite common, there is still the psychologic factor of the "straight jacket" which the patient cannot and does not escape, try as he may. This is something which we must seriously take into consideration.

Sporadic attempts have been made in various parts of the world to manage diabetic patients on "free diets." This is the opposite extreme from the usual practice. There has been some value in these attempts for they have shown that if a patient who has been on a calculated diet is placed on a free diet he will at first "eat his head off"

but finally settles down to a fairly regular routine which will not vary much from day to day. The weakness in this idea is that good therapeutic control of these patients, that is of their glycemic level, was not insisted upon with appropriate adjustment of the insulin dosage. They were allowed to carry on with excessive hyperglycemia. It was assumed that it was impossible to adjust the insulin closely enough to control their diabetic state so little was done and little was accomplished. In this country Tolstoi² has used such free diets without adequate control and in a few decades we shall know the results.

The question confronting medical men treating diabetes is: Can the work with free diets be carried on successfully? Can the patient on such a liberal diet be adequately protected? If adequate protection can be furnished, such a regimen should be beneficial to patients. If it cannot, the procedure should be condemned regardless of the patient's adverse reaction to dieting.

A little over a year ago I was confronted with a serious problem. Owing to overcrowding of our hospitals, some of my patients had to wait four to eight weeks for admission. This, of course, was an intolerable situation for once the diagnosis of diabetes has been made the patient's routine should be started immediately.

The difficulty of obtaining beds in the hospital and also the desire to see what could be accomplished in the management of diabetes outside a hospital stimulated the present research. The questions to be answered were: Is it possible to solve the individual problem of the diabetic in the office without sending the patient to the hospital where all things are controlled? Can the insulin dosage be adjusted closely so that the patient is well protected? Can this be done without teaching him the elaborate methods of calculating diets? This questioning presented a real challenge. If proper control of the patient could be accomplished with only slight regulation of his eating habits, the adverse psychologic

factor connected with dieting would be eliminated.

The policy I inaugurated was to inquire about the patient's eating habits to see whether there was any gross abuse of food. Most persons have fairly well fixed eating habits. They eat much the same kind and quantity of food, day in and day out. The only directions I gave them were as follows: Omit all sugar, pastry and soft drinks. Eat everything else as you always have but avoid stuffing. Do not eat more than two slices of bread with each meal and if you have potatoes eat only one slice of bread. You may have ice cream without any syrup over it once a week but no soft drinks. The rest of the time use fresh fruit, fruit canned without sugar or cheese and crackers for dessert. This seemed to all patients a very simple directive, one they could easily follow. There was no planning, no weighing or measuring of food. This represented only a slight change from what they had been doing in the past decade or more and thus there was no feeling of going on any rigid dietary routine, no feeling of being in a "straight jacket."

In evaluating these instructions one must remember that a diet of 200 Gm. of carbohydrate, 100 Gm. of protein, 100 Gm. of fat, with a total of 2,100 calories, is in fact a normal diet. A patient who eats in a normal fashion, with the slight restrictions mentioned, will not consume any more food. In fact, I believe from the evidence so far that most patients consume less and are happy about the fact that they do not have to be on a "strict diet."

In establishing the routine the patient comes to the office the first day and the blood sugar and urine are examined three times, before breakfast, lunch and dinner, with the patient taking food according to his regular habits. Usually all three blood sugar levels are quite high in which case I administer 20 units of protamine zinc insulin after the evening check-up and advise the patient to come to the office each subsequent morning at 8 A.M. without breakfast. Each morning the fasting blood sugar is

checked and the patient is given 20 units of PZI. The fasting blood sugar yields definite information on the fall of the blood sugar for if the PZI dosage is adequate the fasting blood sugar will be normal. If it is normal, the dose should not be increased for the patient will encounter an insulin reaction. If it stays elevated, the dosage should be increased by 5 units until the fasting blood sugar falls to normal; the patient is kept on that dosage provided there are no insulin reactions. If reactions occur the dosage is reduced by 5 units. Each day the patient is instructed about insulin administration so that by the time his routine is adjusted and the blood sugar in the morning remains normal he knows how to administer the insulin and is on his own.

The next point to determine is whether the blood sugar remains normal throughout the day, that is, before breakfast, lunch and dinner. Sometimes as soon as the fasting blood sugar level is adjusted, usually a week or two later, the blood and urine are checked three times daily before meals. It is ideal if all three blood sugar determinations are normal. If the morning and evening blood sugars are normal and the noon determination elevated, this is still satisfactory for such a patient does not have hyperglycemia more than 25 to 30 per cent of the twenty-four hours. Even a normal individual has a postprandial hyperglycemia, sometimes lasting two hours after each meal, or six hours a day. This is 25 per cent of the twenty-four-hour period and I use this as the standard for comparison in establishing the regimen of the diabetic.

If the morning blood sugar is normal and the noon and evening blood sugar elevated, this calls for additional units of regular insulin in the morning to prevent the postprandial rise of blood sugar following breakfast. This automatically reduces the evening blood sugar level as well. If the fasting blood sugar is above normal, this, of course, calls for an increase in the PZI dosage.

The results of this routine have been quite favorable for almost all the patients

have progressed satisfactorily, with minimal loss of time and disorganization of their lives. The accompanying charts show seventeen patients who have had the longest follow-up. These were unselected, consecutive cases (although the order on the charts is not strictly chronological), showing their course after the preliminary period of adjustment at the office. On the charts this period is marked "daily checks." On Sundays the PZI was omitted as the dates at the top of the charts indicate. Hence the blood sugar usually rose on the following day.

CASE REPORTS

CASE I. A woman, aged sixty-four, was first seen on July 25, 1947, because of glycosuria. The three blood sugars before each meal were 217-282-316, with heavy glycosuria throughout, a faint trace of albumin and acetone 2+. (Fig. 1.) She was 15 per cent overweight and had been as much as 22 per cent overweight. There was no diabetes in the family. The blood pressure was 200 systolic and 100 diastolic. The blood sugar came down to normal on the third day (she had 25 units of PZI the first evening) and stayed at a normal level during twelve days of administration of insulin in the office, with the exception of August 4th following a Sunday on which insulin was omitted. At the end of this period all three blood sugars were normal and all insulin was discontinued. The next check-up, twenty days later, showed that all three blood sugar determinations were normal as did all subsequent checks.

One might say that this elderly woman might have been adjusted without insulin, but with a low diet it could not have been done so quickly nor with the same comfort to the patient. Also there is the psychologic advantage that having had insulin once even though her blood sugar has remained normal for eight months she knows that if she is careless she would have to go back to taking insulin. No patient wants this if it can be avoided.

CASE II. A Negro woman, aged fifty-two, had been losing weight and glycosuria had been discovered ten days previously after a bad cold. She was drinking much water and had polyuria and nocturia. Her mother and paternal uncle were diabetic. She was 19 per cent overweight and had been 31 per cent overweight. The blood pressure was 150 systolic and 80 diastolic.

On January 15, 1947, the three blood sugar determinations were 234-467-508, with a heavy glycosuria throughout and an albumin of 1+. (Fig. 1.) The first evening I gave her 15 units of insulin and 20 units of PZI and the following mornings 20 to 25 units of PZI. The blood sugar

in the evening on a dosage of 23 units of PZI. Subsequent PZI dosage has fluctuated between 22 and 28 units and subsequent check-ups have shown a good control for a year. It is obvious that she needs insulin despite her age. At the last examination on February 16, 1948, the

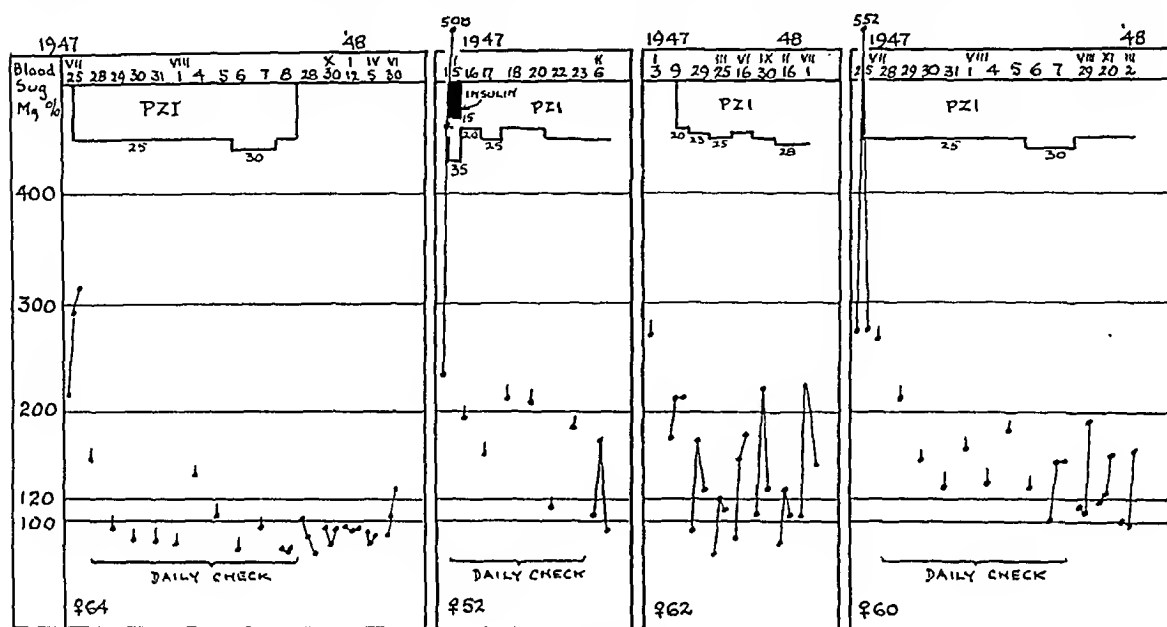


FIG. 1. Cases I to IV.

fluctuated somewhat and the fasting blood sugar was not normal until the twenty-second day. A recheck two weeks later showed satisfactory levels of blood sugar, 105-176-91. She was then taking 25 units of PZI which was reduced to 15 units. She has not been seen since.

CASE III. A nurse, aged sixty-two, had had symptoms of diabetes for a month. A fasting blood sugar taken elsewhere was 271 mg. per cent, with the urine showing 4+ sugar. She was placed on a diet; she lost weight and the glycosuria disappeared. When I saw her on January 9, 1947, the glycosuria had reappeared. (Fig. 1.) She was 1 per cent underweight but had been 17 per cent overweight previously. A maternal cousin was diabetic. The blood sugars were 175-213-214, with heavy glycosuria throughout the day; no albuminuria was present. Since she was a nurse, it was not necessary to have her come to the office daily so I directed her to take 15 units of PZI each morning and to increase this by 2 units each subsequent morning until she encountered a reaction at which time she was to reduce the dosage by 2 units. I saw her a week later when the blood sugars were 91-174-130, with only a slight glycosuria at noon and

three blood sugar determinations were 79-130-107.

CASE IV. A woman, aged sixty, reported that diabetes had been discovered four years previously. On a restricted diet glycosuria disappeared but symptoms of diabetes reappeared following an attack of influenza. She was 7 per cent overweight and had been 23 per cent overweight. There was no diabetes in her family. The blood pressure was 226 systolic and 120 diastolic. On July 25, 1947, the blood sugars were 272-552-275, with heavy glycosuria throughout, albumin 1+ and no acetone (Fig. 1.) She was given 25 units of PZI that same evening and each subsequent morning she received 25 units of PZI for nine days, with the fasting blood sugar dropping slowly toward normal. On the last day at the office the three blood sugars were 100-98-155, with only a trace of glycosuria in the evening. Her PZI was then reduced to 25 units upon which she continues. Subsequent checks have shown quite good control for eight months.

CASE V. This chart (Fig. 2) shows an interesting record over a period of twenty-five years. In 1923 when this patient was thirty-six years

old she came to see the author because of glycosuria. Her fasting blood sugar was checked; this was normal and there was no glycosuria. A glucose tolerance test the next morning showed a prediabetic curve, with the blood sugar not reaching normal for three hours and a quarter.

and had been 24 per cent overweight. The blood pressure was 118 systolic and 90 diastolic. There was no diabetes in her family. The patient had five children and had not been ill except for colds.

All three blood sugar levels were quite high.

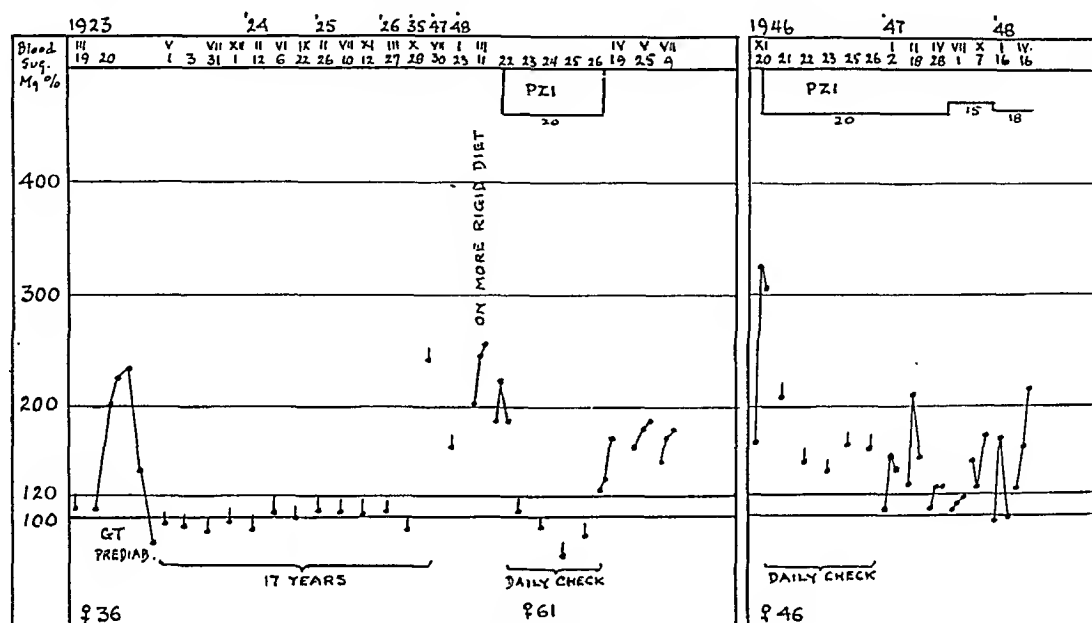


FIG. 2. Cases v and vi.

Afterward she watched her diet somewhat and a fasting blood sugar was determined periodically for twelve years. All these determinations were normal and glycosuria appeared but once during this period. The question in such a case is whether the patient will eventually become diabetic. Twenty-four years after she had first shown a prediabetic type of glucose tolerance curve, in 1947 and 1948, she had two more blood sugar tests taken elsewhere. Both of these showed elevation. When she came to see the author on March 11, 1948, the check-up showed blood sugars of 202-241-254, with no glycosuria in the morning but 2+ at noon and in the evening. The next day the blood sugar levels were 187-232-185. Twenty units of PZI were administered that evening. The blood sugar dropped promptly to normal the next morning and stayed normal the next four days at which point the PZI was discontinued. She is now sixty-one years old and the insulinogenic weakness revealed twenty-five years ago has come to the foreground in frank diabetes.

CASE VI. A woman, aged forty-six, had classical symptoms of diabetes. The discovery of glycosuria had been made one week before I saw her. She was then 12 per cent overweight

(Fig. 2.) I gave her 20 units of PZI the first evening and beginning the next morning she received 20 units of PZI with a blood sugar check at noon each day for six days. After that she took 20 units of PZI each morning at home and the blood sugar level came down to normal throughout the day in the fifth month. It stayed at normal for three months after which there was a slight rise which did not become significant until April, 1948 at which time the dosage of 18 units of PZI was increased to 20 units.

CASE VII. A man, aged sixty-three, had glycosuria discovered nearly a year earlier. He had been on a 1,500 calory diet and became sugar-free but he had lost much weight and was feeling depressed. He had nocturia, three times during the night. He was 14 per cent overweight and had been 55 per cent overweight. His blood pressure was 140 systolic and 80 diastolic. There was no diabetes in his family. The glucose tolerance test on April 30, 1940, was performed before I saw him and showed a frank diabetic curve. The fasting blood sugar on May 14th was 187 mg. per cent. When he came to me, he was taking 40 units of PZI and on June 21st the blood sugar levels were 100-143-130, with no glycosuria. (Fig. 3.) The dosage

was reduced to 30 units of PZI, later to 28 units, and the subsequent checks all showed good control. During this time he was on an ordinary diet of his own choosing. On October 25th all insulin was discontinued but a check thirteen days later showed a considerable rise of the blood

with heavy glycosuria throughout; no albumin or acetone were present. (Fig. 3.) She was on a low diet at first but there was no response. Hence on December 1, 1947, she was started on the regular office routine with administration of PZI and the blood sugar dropped promptly to

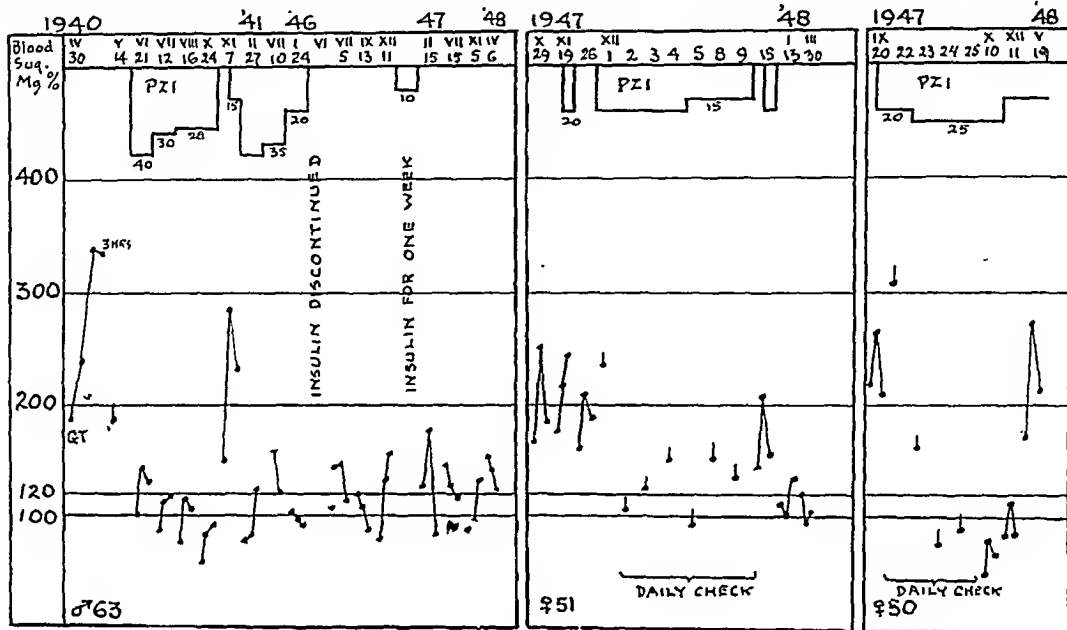


FIG. 3. Cases VII to IX.

sugar so he was again placed on PZI, with a prompt response. All insulin was again discontinued eight months later. Since then, with the exception of a small dose of 10 units for a week in December, 1946, he has had no insulin and the diabetes has been well controlled even though he has been somewhat careless with his diet. His weight has increased from 180 pounds to 221 pounds and he has led a normal life in every way.

Although this patient is an elderly man, at the outset neither a low diet nor diet plus insulin controlled the diabetes adequately. Systematic check of the blood sugar three times a day yielded definite information as to how much insulin was required. When the diabetes had been controlled for a time, the insulin could be completely discontinued.

CASE VIII. Glycosuria had been found in a woman, aged fifty-one, a few days before she consulted me and she had had classic symptoms of diabetes for two weeks. She was 7 per cent overweight and had been 14 per cent overweight. The blood pressure was 146 systolic and 90 diastolic. There was no history of diabetes in her family. On her first check-up on October 29, 1947, the blood sugar levels were 167-250-184,

normal. After nine days all insulin was discontinued. A check-up a week later showed some elevation of the blood sugar and 20 units of PZI were administered that evening only. No insulin has been given since and her condition has remained in perfect control.

CASE IX. A woman, aged 50, had had diabetic symptoms for several weeks and glycosuria had been discovered a few days previously. She was 12 per cent underweight and had never been overweight. The blood pressure was 112 systolic and 76 diastolic. There was no diabetes in her family. She had had two thyroidectomies in the past. On September 20, 1947, the blood sugar determinations were 219-263-210, with heavy glycosuria throughout; no albumin and acetone 3+ were present. (Fig. 3.) The PZI routine was started immediately and with the exception of the following morning the blood sugar level dropped promptly and stayed down throughout the day as shown by subsequent checks. The follow-up in the office lasted only four days. She is now taking 15 units of PZI daily.

CASE X. A woman, aged fifty-six, had been placed on a reduced diet because she had had glycosuria, and a fasting blood sugar a week

before I saw her was reported as 289 mg. per cent. On May 23, 1947, she was 24 per cent overweight and had been 36 per cent overweight. A maternal cousin was known to be diabetic. The blood pressure was 160 systolic and 100 diastolic. She had had virus pneumonia three

checks have shown normal blood sugars and she is now on 18 units of PZI; at the last examination this was reduced to 12 units. This patient could manage now without insulin except for the fact that she is quite careless about her diet and drinks considerably.

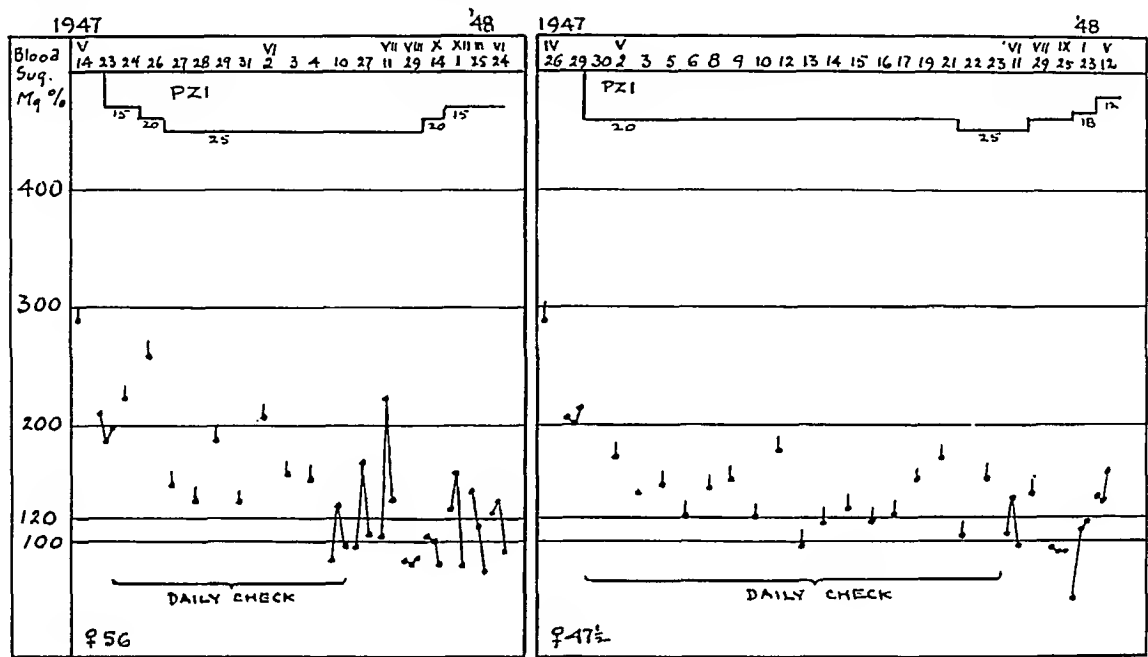


FIG. 4. Cases x and xi.

years earlier. The blood sugars were 210-184-197, with heavy glycosuria throughout on the reduced diet. (Fig. 4.) The first evening she was given 15 units of PZI. This was increased to 20 and later to 25 units; the blood sugar level did not fall to normal for two weeks. The office routine was continued for twenty-two days, but the results as judged by subsequent checks were quite gratifying on a continually reduced dosage of PZI.

CASE XI. A woman, aged forty-seven, had been excessively thirsty for six months and glycosuria was found, with a fasting blood sugar level of 289 mg. per cent. There was no diabetes in her family. She had had a hysterectomy twenty-five years previously. She was 10 per cent overweight and had been 26 per cent overweight. The blood pressure was 190 systolic and 110 diastolic. On April 29, 1947, the blood sugar determinations were 206-202-214, with heavy glycosuria throughout, no albumin and a faint trace of acetone. (Fig. 4.) The office routine was started the following day with 20 units of PZI. This was continued for twenty-four days before the blood sugar level became normal on 25 units of PZI daily. Subsequent

CASE XII. A woman, aged sixty-five, consulted the author because of recent glycosuria. Her mother, sister and brother were diabetic. She was 5 per cent underweight and her highest weight had been only 4 per cent above normal. Her blood pressure was 180 systolic and 96 diastolic. The first examination made on August 7, 1947, (Fig. 5) showed the following values for the blood sugar: 164-303-285; the urine sugar was 0, 1+ and 3+. Twenty units of PZI were administered that evening; then the PZI was increased to 30 units and the blood sugar dropped promptly so that after six days all insulin was discontinued. Subsequent checks have been normal.

CASE XIII. Glycosuria had been found eight months previously in a man aged thirty-four. On April 17, 1947, he was 22 per cent overweight and had been 36 per cent overweight. There was no diabetes in his family. The blood pressure was 134 systolic and 90 diastolic. The blood sugar levels were 117-147-230, and the urine showed a faint trace, 0 and 2+ sugar, with heavy albuminuria. (Fig. 5.) He was given 20 units of PZI the first evening and the two subsequent mornings. Three weeks later, on

20 units of PZI, the three blood sugars were normal and remained normal for four months. About that time he began to drink considerable quantities of beer and the next two examinations showed the result. His weight increased by 25 pounds. After this demonstration he is now

been discovered a few days before on a routine examination. She had been thirsty for a month and had been losing weight. She was 4 per cent underweight and had never been more than 3 per cent overweight. A paternal cousin was a diabetic. Her blood pressure was 110 systolic

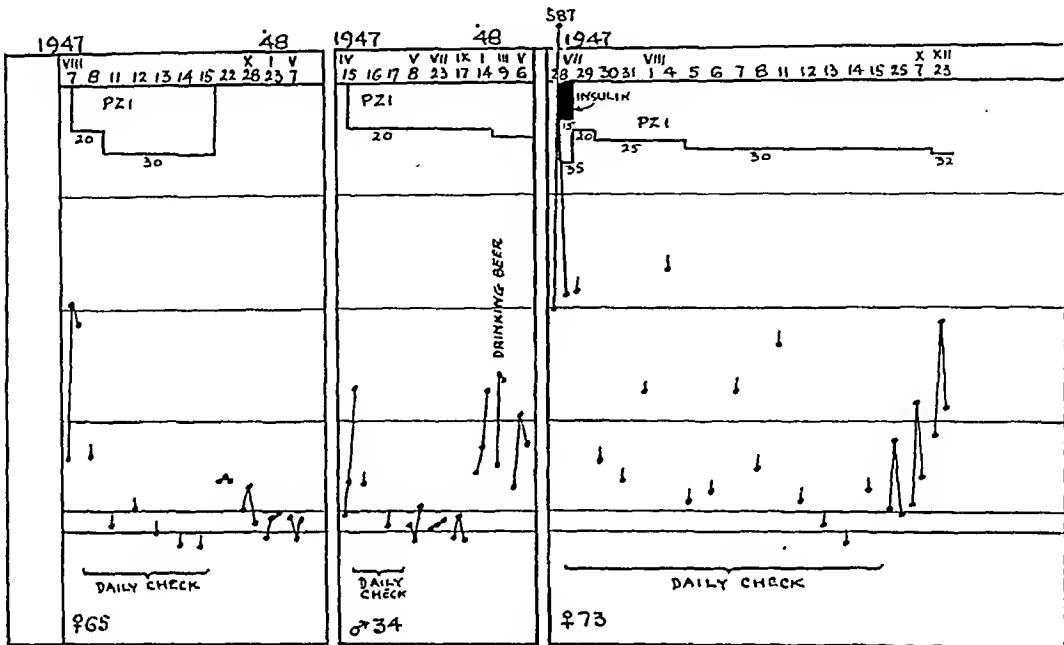


FIG. 5. Cases XII to XIV.

taking no beer and subsequent check-ups should show the result.

CASE XIV. A woman, aged seventy-three, had had glycosuria seven years previously with classic symptoms of diabetes. On July 28, 1947, she consulted the author because she again had been having nocturia and had lost weight. She was 14 per cent overweight and had been 45 per cent overweight. Her father and sister were diabetic. Her blood pressure was 144 systolic and 80 diastolic. The first check-up showed the blood sugar levels to be 300-587-313. The urine showed heavy glycosuria throughout; no albumin and acetone of 1+. That evening she received 15 units of insulin and 20 units of PZI and then started the office routine which was continued for fourteen days at which time the fasting blood sugar was normal. A check-up ten days later showed good control. Five weeks later the blood sugars were somewhat elevated but not seriously for her age. However three months later, on 32 units of PZI she was definitely out of control and the dosage was increased to 36 units.

CASE XV. A woman, aged twenty-eight, consulted me because of glycosuria which had

and 70 diastolic. The first check-up on November 17, 1947, showed blood sugars of 192-258-340, with heavy glycosuria throughout, no albumin and a trace of acetone. (Fig. 6.) She received 20 units of PZI that evening and 20 units of PZI each morning for seven days. The blood sugar came down promptly. The first recheck, a week after the daily examinations in the mornings, showed a slight elevation of blood sugar without any PZI that morning and so she received a dose that evening. However, after that single dose all PZI was discontinued for two weeks when a recheck showed the same slight elevation of the three blood sugars. Another trial with PZI was made and nearly three weeks later there was greater elevation of the three blood sugars and as a result she resumed taking 20 units of PZI each morning.

CASE XVI. A man, aged sixty-three, had glycosuria which had been discovered three weeks earlier. There was no familial history of diabetes. He was 15 per cent overweight and had been 29 per cent overweight. The blood pressure was 162 systolic and 106 diastolic. The first check-up on January 20, 1948, (Fig. 6) showed blood sugars of 306-275-250, with heavy

glycosuria throughout, a faint trace of albumin and no acetone. Twenty units of PZI were given that evening and later 25 units of PZI each morning for the next ten days. He continued taking 25 units of PZI each morning and on March 10th all three blood sugars were normal and he is continuing on the same routine.

done in the past, thus upsetting his mental equilibrium and creating needless psychologic problems. If the patient is allowed to regulate his own restrictions, all that is necessary is adjusting the insulin dosage to that routine and the patient will be happy. When a "fixed routine" is imposed on him,

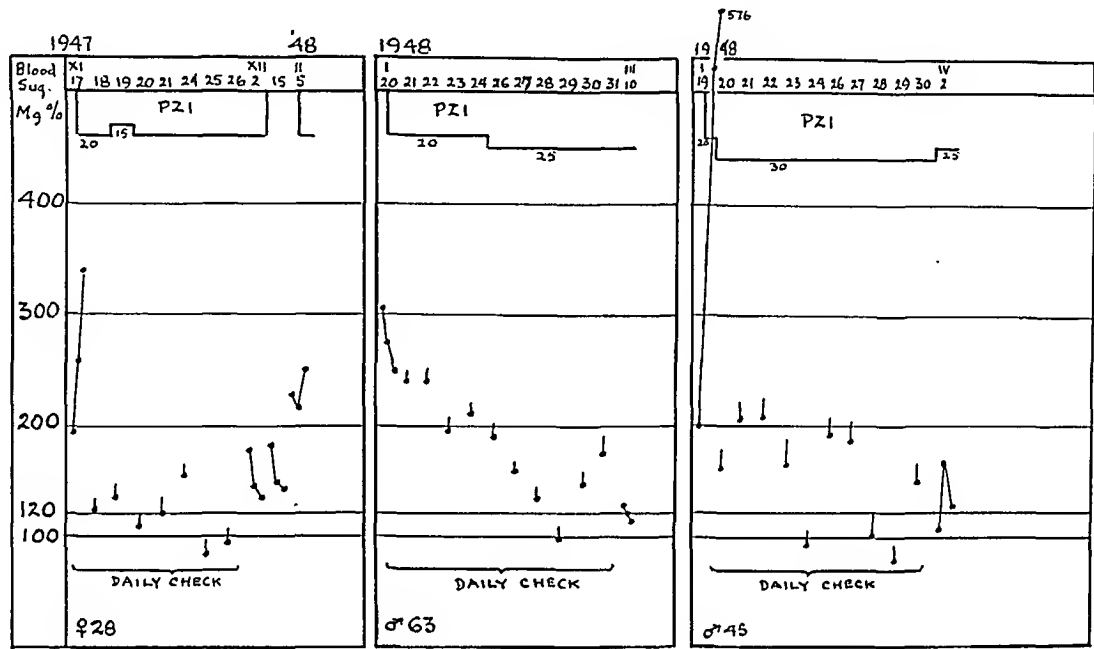


FIG. 6. Cases xv to xvii.

CASE xvii. A man, aged forty-five, had known of glycosuria for two months. There was no history of diabetes in his family. He was 14 per cent underweight but had been 30 per cent overweight. The blood pressure was 116 systolic and 70 diastolic. On January 19, 1948, the blood sugars were 201-522-576, with heavy glycosuria throughout, a trace of albumin and no acetone. (Fig. 6.) After the usual evening dose of 20 units of PZI he received 30 units of PZI each morning for the next ten days. A check-up two months later, on 25 units of PZI, showed virtually normal blood sugar levels with glycosuria persisting. He is now continuing on 20 units of PZI.

SUMMARY AND CONCLUSIONS

A study of the progress of a group of patients shows that a diabetic can live on a practically normal diet such as he has been accustomed to all his life with only a few proscriptions. There is no need for completely reorganizing his life, as has been

additional problems are created and the patient is not happy. It matters little if the difference between a fixed routine and the elective routine is from 100 to 300 calories since whatever the voluntary choice of food by the patient the insulin is adjusted to care for it.

I am not advocating a "free diet" and "careless control" but an almost free diet with adequate control as reflected in the blood sugar level throughout the day, not merely in the fasting blood sugar. If the fasting blood sugar is normal, the noon sugar elevated and the evening blood sugar normal, this is acceptable. If the fasting blood sugar is normal and the noon and evening levels high, some insulin should be added to the PZI in the morning to take care of this postprandial rise. If all three blood sugars are elevated, the PZI should be increased and the subsequent check up will show whether or not some insulin should be added to the PZI. Both insulins

should be given in the same syringe, in one injection, so as to diminish the discomfort. It does not matter whether some of the insulin is changed over to PZI. The important thing is not "how much of the insulin is changed over" but "how it works." Only in this way can the patient's individual problem be solved satisfactorily.

With such a regimen the patient loses no time from work. By losing no time he also loses no income. The cost of his treatment is also greatly reduced and he is not overburdened with impractical details which disturb his equanimity. His problem is

reduced to the absolute minimum and the burden of it rests largely in the hands of the physician guiding him. Furthermore, this regimen relieves pressure on hospital beds which today are needed more urgently for other types of cases.

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Fatal Anuria, the Nephrotic Syndrome and Glomerular Nephritis as Sequels of the Dermatitis of Poison Oak*

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THE dermatitis of poison oak (*Rhus toxicodendron diversilobum*) is generally considered to be an annoying but benign episode. When mentioned at all by patients, it is not often accorded the dignity of a place in the physician's notes. This is particularly true when these notes describe the details of graver illness appearing more recently than the dermatitis. Such refusal to take the disorder seriously may account, at least in part, for inability to find modern reports of complications following poison oak dermatitis; the older literature contained an occasional but inadequately documented report of death.

There are at least two reasons for expecting that complications might arise after the dermatitis of poison oak. Obviously, the broken skin could serve as portal of entry for infection with all of its potentialities in production of disease. Secondly, and apparently less well known, the provocative agent is one which causes sensitization.

In view of current conceptions of the parts played by infection and sensitization as etiologic factors in nephritis and periarthritis nodosa, it may be of interest to record some instances in which renal complications appeared in several patients as the dermatitis of poison oak was healing. In one there was fatal anuria with severe degeneration of renal tubules. In four the nephrotic syndrome was prominent; pure lipoid nephrosis seemed a likely diagnosis in three of these, chronic glomerulonephritis in one. In two additional cases, with suspected and probable streptococcal infection, the syn-

dromes resembled the onset of glomerular nephritis; there was considerable tubular degeneration in one of these. Still another patient has been observed in whom the features of the initial stage of glomerular nephritis followed the dermatitis of poison oak; in this case the diagnosis was thought to be periarthritis nodosa and the report will be presented elsewhere¹ together with a verified case of periarthritis nodosa following the closely related primrose dermatitis.

CASE REPORTS

CASE 1. Mr. L. P. (E33251), a wood-pattern maker fifty-four years of age, entered Stanford University Hospital in uremia on June 30, 1943.

One daughter was highly susceptible to the dermatitis of poison oak, but not so the wife and another daughter. The mother, father and a sister died of cancer.

He had suffered many severe bouts of poison oak acquired on slight exposure. Because of one attack in 1942 he took to bed for two weeks. A routine life insurance examination was successfully passed within the previous ten years. There had been no exposure to heavy metals and he had taken no medicines. His health generally had been good.

While in Sierra Nevada on May 30, 1943, he gathered and carried wood which smoked badly when burned; he was also exposed to the smoke. He soon had severe dermatitis, with vesicles on face and neck by June 3rd, when the eyelids were swollen (without eruption or irritation on the lids). A cough producing about 15 cc. of greenish-yellow sputum daily began on June 7th, and on the following day he was nauseous, vomited and went to bed. On June 9th a physician found moderate edema of the

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face and ankles and on the neck a very slight dermatitis which soon disappeared. The cough improved but the legs ached. Thiamin and unidentified medicines for the skin were given, but not sulfonamides. About this time the urine became scant but not smoky or bloody, and it was found to contain many casts and much protein but few erythrocytes. There was an anuria for a day on June 15th when arterial pressure and a blood count were normal and the concentration of urea in the blood was 54 mg./100 cc. Nausea and vomiting increased, oliguria continued and he entered the hospital after a day or two of rapidly progressing dyspnea.

He was very ill and semi-comatose, lying flat and with deep, rapid respiration. Nutriture and development were good. There was no fever. The optic fundi were normal; the eyelids were slightly puffy and the buccal mucosae were dry. The jugular veins were not distended. The heart was enlarged only slightly or not at all and was regular at a rate of 70. The sounds were normal, without gallop, rub or murmur; the second sound was louder at the pulmonic area than at the aortic area. The lungs were clear. The abdomen was entirely negative. The back of the trunk was normal. Arterial pressure was 130/90 mm. Hg. There was a very slight trace of ankle edema, and a few small, almost healed patches of dermatitis were found on the neck.

The concentration of hemoglobin was 16.8 Gm./100 cc., and there were 5,370,000 erythrocytes and 7,100 leukocytes per cu. mm.; 90 per cent were polymorphonuclear neutrophils, 7 per cent lymphocytes, and no eosinophils were counted. Urine for twenty-four hours measured only 160 cc. and contained 7.2 Gm. of protein, 20,000,000 casts (none of red blood cells, 20 per cent waxy and granular, and 80 per cent broad), 10,000,000 erythrocytes, and 50,000,000 leukocytes and renal tubular epithelial cells of which 5,000,000 were oval fat bodies. Concentration of urea in the blood was 455 mg./100 cc.

An electrocardiogram showed left axis deviation, a P-R interval of 0.20 and a QRS duration of 0.14 seconds with atypical bundle branch block. Fluoroscopy revealed a heart of normal size and clear lungs with no pleural fluid.

Digitalis glycoside was given by vein although the dyspnea was probably that of acidosis. An infusion of 5 per cent glucose in 500 cc. of saline was followed the next day by 1,500 cc. of 10 per cent glucose in distilled water. Oliguria per-

sisted, with slight edema of the sacral region and hands. Arterial pressure was 140/85 mm. Hg. He ate poorly and complained of low backache without associated objective findings. On July 2nd the concentration of urea in the blood was 488 mg. per 100 cc. and he had four liquid, non-bloody stools. On the following morning dyspnea increased suddenly without tachycardia or other changes, and he soon became comatose, pulseless and died.

The autopsy was performed six hours after death.* There were 600 cc. of clear fluid in the left pleural cavity and 700 cc. in the right. The peritoneal and pericardial cavities did not contain abnormal amounts of fluid. The heart weighed 340 Gm. and was normal. The liver weighed 1,830 Gm. and was somewhat hyperemic. The hepatic cells toward the centers of the lobules were rather small but otherwise not remarkable. There was a small benign carcinoid tumor of the rectum and a microscopic adenoma of the adrenal cortex. The thyroid gland weighed only 8 Gm. after formalin fixation. Within it were large amounts of dense fibrous tissue infiltrated by numerous lymphocytes. This tissue separated the unusually small, empty follicles into irregular lobules. Widespread degeneration of individual fibers was seen in histologic sections of the psoas muscles and no cause could be demonstrated. There were scattered leukocytes, a few of which were eosinophiles.

The kidneys weighed 200 and 240 Gm. respectively. The surface of both was smooth and grayish-red. The cortex was 7 to 8 mm. thick and its cut surface presented some indistinct narrow red and yellowish streaks running perpendicular to the surface. A small tubular adenoma, 2 mm. in diameter, was present in one medullary pyramid on the left side. Most of the glomeruli appeared normal in histologic sections although in some there was irregular swelling and focal increase in the number of epithelial cells over the inner surface of Bowman's capsule as well as over the capillary tufts, a few of which were indistinctly separated from the capsules. Several well developed epithelial crescents were seen. (Fig. 1A.) Some glomerular capillaries were dilated and contained numerous erythrocytes, but azocarmine-aniline blue stain showed no thickening of the glomerular capillary membranes. A few glomeruli

* I am indebted to Dr. Alvin J. Cox, Jr. for the autopsy description.

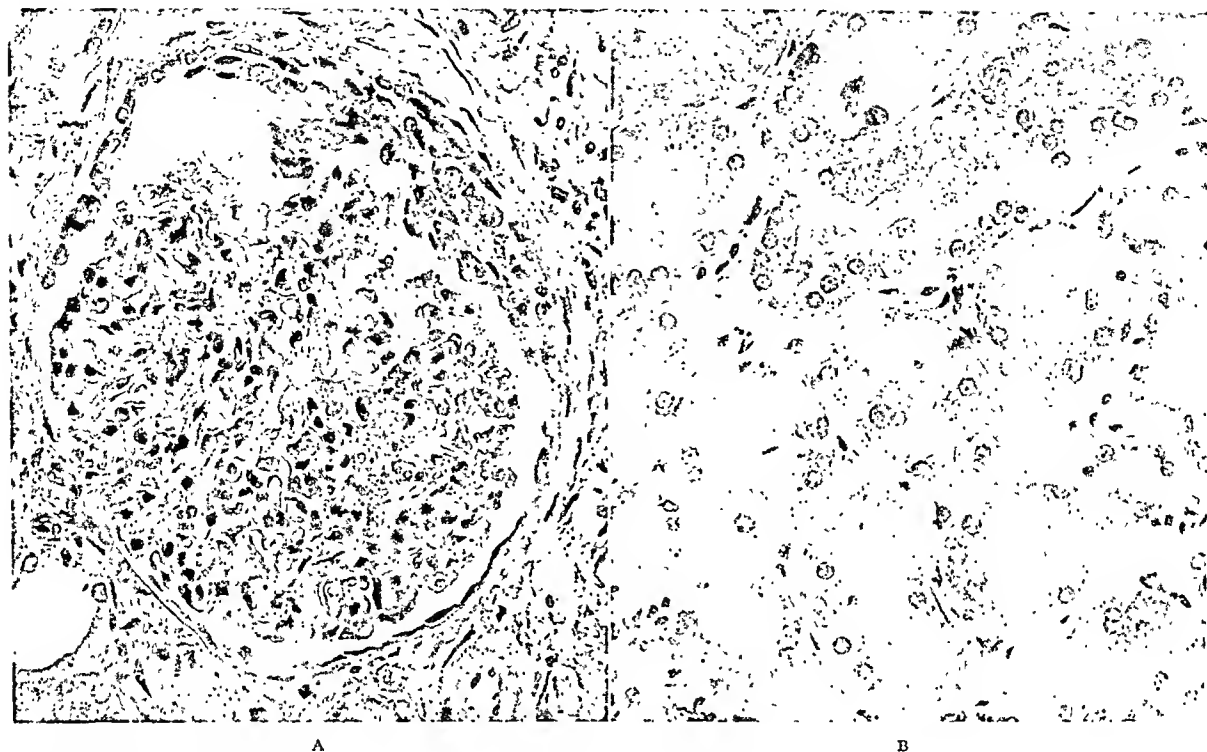


FIG. 1. Case 1. A, glomerulus with epithelial crescent. B, small multinucleated projecting cytoplasmic masses in tubular epithelium.

completely replaced by fibrous tissue were probably unrelated to the terminal disease.

The tubules likewise showed focal changes. The epithelium of the proximal convoluted tubules was considerably swollen in many places, and the cytoplasm was more granular than usual. Only a few small colloid droplets could be seen. In a few places the swelling was more marked and nuclei were not visible or were hyperchromatic. Many of these cells had desquamated. Other convoluted tubules were smaller than normal and were frequently lined by flattened cells. A number of the tubules in the cortex had small multinucleated projecting cytoplasmic masses in the epithelial lining like those seen during epithelial regeneration. (Fig. 1B.) About 5 per cent of the sections of tubules contained hyaline or granular casts and in a few there were masses of partly disintegrated erythrocytes. Occasional tubules showed fine lipid droplets in the cytoplasm of the lining cells but most were free from fat histologically. In scattered places within small tubules of both the cortex and the medulla there were small rounded conerctions of slightly refractile transparent material which was stained by hematoxylin but did not give the reaction of calcium with the Von Kossa staining method. In several of these there were clusters of fine, needle-like

structures suggesting crystals. The significance of these has not been determined.

The arteries in the kidneys were normal except for mild intimal fibrous thickening in some of the medium sized branches. The interstitial tissue of both the cortex and medulla contained a few scattered lymphoid cells and there were occasional small lymphoid nodules. The tubules of the medulla were somewhat separated from one another by more than the usual amount of fibrous interstitial tissue.

Almost all of the morphologic kidney lesions were in the tubules where there was evidence of injury to the epithelium and some regeneration. The swelling and proliferation of the glomerular epithelium was presumably related. The lesions were less striking than might be expected in view of the fatal anuria. In the autopsy protocol there is a statement that no heavy metals could be demonstrated in the kidney, but the actual records of the toxicologist could not be found.

CASE II. Mrs. D. T. (E7874), a housewife twenty-nine years of age, entered Stanford University Hospital on January 24, 1939, because of edema for one month.

There was no family history of asthma, hay fever, eczema or urticaria. However, the patient's mother, sisters and an uncle had had poison oak repeatedly on slight exposure. In

1946 the patient's daughter had poison oak at the age of five; a son aged three had escaped the dermatitis.

The patient began to have hay fever and bronchial asthma at the age of five; epinephrine had been injected frequently. She had severe

headache and vomiting on December 29, 1938; swelling of the eyelids was noted within a few days and generalized edema soon appeared without other symptoms as the body weight increased between 15 and 30 pounds. There was no gross hematuria then or at any other time.

TABLE I
FINDINGS IN CASE II

Date	Rate of Excretion in Urine per Twenty-four Hours				Arterial Pressure (Mm. Hg)		Blood		
	Protein (Gm.)	Casts* (Thousands)	Red Blood Cells (Millions)	White and Epithelial Cells (Millions)	Systolic	Diastolic	Hematocrit (% normal)	Urca (Mg./100 cc.)	Serum Protein (Gm./100 cc.)
January 24, 1939.....	5.9	1200	1	25	115	80	116	15.0	5.1
January 31, 1939.....	11.6	500†	0.5	7	110	85	111	18.7	4.8
February 16, 1939.....	7.2	400	5	20	19.5	...
March 2, 1939.....	8.4	3500‡	3	16	105	80	99	16.0	5.1§
March 29, 1939.....	3.0	2000	5	7	120	85
May 4, 1939.....	2.4	900	6	4	110	80	91	21.3	5.7
May 18, 1939.....	0.2	400	4	3	105	70	90	17.8	6.2
June 15, 1949.....	0.08	30	2	2	90	19.5	6.3
July 11, 1939.....	0.00	0	1	2	110	65	90	19.5	5.7
August 24, 1938.....	0.01	0	1	1	105	70	89	6.6
October 16, 1939.....	0.00	0	0	4	125	80	90
November 30, 1939.....	0.00	0	0	3	120	80	90	19.6	...
December 21, 1939.....	0.00	0	0	5	120	80
February 21, 1940.....	0.00	0	0	2
September 4, 1940.....
October 20, 1946.....	0.00	120	80

* All hyaline casts.

† Some with a few fat droplets.

‡ Some with many fat droplets.

§ Serum visibly lipemic.

dermatitis of poison oak almost annually for many years; it usually appeared in December or January, often by exposure to her husband's hunting clothes. About 1930 the ingestion of a commercial extract of poison oak was tried in an attempt at prophylaxis but was discontinued when it caused an eruption of the lips and mouth. A similar but more careful trial with a very dilute extract in 1946 appeared to be efficacious, at least it was not obviously harmful. In January, 1937, a most severe attack occurred, with "one solid blister from shoulder to wrist" on both arms; recovery required months and scars remained almost a year. Hematuria had never occurred; a routine urinalysis was negative on March 16, 1936.

The pertinent illness began with one day of

The last previous attack of poison oak had started in December and was not particularly severe.

Examination showed massive pitting edema and two small healing lesions of poison oak. The optic fundi and heart were normal; arterial pressure was 115/80 mm. Hg.

Table I gives the results of laboratory findings and indicates the course of the illness. It may be noted that microscopic hematuria never rose above 6,000,000 erythrocytes per twenty-four hours (voided specimens) and that there was relative hemoconcentration at first. Visible lipemia was present only in serum taken March 2, 1939, when fat was present in the urine as droplets in hyaline casts and as oval fat bodies. Arterial pressure ranged irregularly from 120/85

to 105/70 mm. Hg, and the concentration of urea in the blood from 15.0 to 21.3 mg. per 100 cc. The blood Wassermann reaction was negative, the blood group A.

A diet was prescribed and potassium chloride given without benefit. Returning home after only a few days in the hospital, she was ambulatory thereafter. More than the usual amount of asthma appeared until late in March and again during August; epinephrine was used freely. The greatest part of the diuresis occurred during April.

The first of two uncomplicated pregnancies began in June, 1940. In February of 1947 she continued to be well, with normal urine; there have been only very minor attacks of poison oak. Serum taken January 31, 1947, agglutinated sheep cells in a titer of only 14.

CASE III. L. C. F., a school boy twelve years of age, was seen on March 27, 1934, by Dr. Thomas Addis, who kindly supplied the following information:

There was no familial hypersensitivity but for hay fever in a cousin. The patient had laryngitis at the age of two, diphtheria at three, otitis media at four, pertussis at five, chicken pox at six and measles at nine. He had several episodes of poison oak. Urinalyses were normal.

About April 10, 1933, he was exposed to poison oak; by evening the skin of face and arms was "blotchy red." On the following morning his face was swollen and he was given an extract of poison oak orally. Within two days there were numerous bullae and generalized swelling. He improved for a few days but a week after the onset became drowsy, vomited and was anorexic. A few days later swelling of the eyelids, abdomen and ankles was noted; the urine was scanty and dark. Proteinuria was discovered April 24, 1933.

Upon admission into a hospital that day it was reported that there was slight edema of eyelids and ankles, exfoliation of the skin on the hands and an arterial pressure of 150/85 mm. Hg (128/70 three days later). There were 4,500,000 erythrocytes and 11,000 leukocytes per cu. mm. of blood: of the latter 66 per cent were polymorphonuclear neutrophils and 6 per cent eosinophils. The urine was clear and yellow with specific gravity 1.008; there was a moderate amount of proteinuria and the sediment contained many hyaline and a few granular casts, a few erythrocytes and leukocytes. The blood contained 29.3 mg. of non-protein nitrogen and 237 mg. of cholesterol per

100 cc.; the concentration of protein in the serum was 4.7 Gm./100 cc. (albumin 3.3, globulin 1.4).

Findings were similar in two later hospital entries. Ascites appeared. The skin was pale but otherwise normal. Arterial pressure varied from 135/90 to 112/78 mm. Hg. Most urinalyses revealed no erythrocytes but there were casts and heavy proteinuria. Acacia given intravenously was followed by reactions with urticaria and fever; these and an intercurrent pharyngitis seemed to precede moderate diureses.

On March 27, 1934, Dr. Thomas Addis found the urine to measure 304 cc. per twenty-four hours; in this period there were 15,200,000 casts (1 per cent fatty, 1 per cent waxy, and 98 per cent hyaline with fat droplets), 600,000 erythrocytes, 24,000,000 leukocytes and renal epithelial cells, and 11.8 Gm. of protein; the specific gravity was 1.032.

Further details are lacking, but apparently the renal lesion continued with edema present most of the time until near the end. Death occurred on February 9, 1935, following urcemia. Necropsy was not permitted.

CASE IV. Mrs. M. G. (241047), a housewife, was twenty-nine years of age when she first entered Stanford University Hospital on April 19, 1945, because of edema for ten months.

No suggestion of the hypersensitive state was obtained in either the family or her own history.

In June, 1944, she had an intensely itching papular eruption on cheeks and a forearm which healed after four days. The dermatitis was attributed to poison oak, known to be present near her home; however, the dermatitis of poison oak had never occurred before and there had been none since. Therapy consisted only of calamine lotion. Within two to four weeks of the dermatitis the legs began to swell; there had been no sore throat or other preceding illness, and there was no gross hematuria at any time. Proteinuria was soon discovered; this and varying degrees of edema continued up to the time of her admission.

Examination in April, 1945, showed pallor, massive pitting edema and minimal ascites. Arterial pressure was 140/96 mm. Hg. The heart, optic fundi, peripheral arterics and skin were normal.

The concentration of hemoglobin in the blood was 14.0 Gm. per 100 cc. Counts showed 4,480,000 erythrocytes and 14,320 leukocytes per cu. mm.; only 2 per cent of the latter were eosinophils. The total concentration of the

serum proteins was 4.86 Gm./100 cc., that of albumin 1.43 Gm./100 cc. The serum was inconstantly lipemic; the cholesterol content was 370 mg. per 100 cc. The concentration of urea in the blood was 36 mg./100 cc. Electrocardiograms were normal. The patient belonged to blood group O₂Rh₁.

In the urine of March 20, 1945, Dr. Thomas Addis found 13.8 Gm. of protein, 2,400,000 hyaline casts, 1,500,000 erythrocytes, and 38,000,000 leukocytes and epithelial cells per twenty-four hours. There were a few oval fat bodies and fat droplets. Two years later the urine contained 10.7 Gm. of protein, 300,000 hyaline casts, 5,000,000 erythrocytes, and 15,000,000 leukocytes and epithelial cells per twenty-four hours. Many voided specimens of urine in the two years showed similar findings; the greatest number of erythrocytes per twenty-four hours was 16,000,000.

Agglutinins for sheep cells were present in a titer of 14–28 on October 15, 1946 and March 20, 1947. On January 3, 1947, Dr. Sidney Raffel found agglutinins in a titer of 128, hemolysins 64; neither antibody was absorbed by heated ox cells. The antistreptolysin titer was 50 units per cc. twice in 1947.

Despite continuing proteinuria and edema, her general status is satisfactory three years after the onset of the disease. Ambulatory most of the time, she has entered the hospital over twenty times for infusions of plasma or human serum albumin. These have been successful in inducing diuresis. Arterial pressure has varied between 130/72 and 160/110 mm. Hg but is not increasing. The most recent concentration of urea in the blood was 27 mg./100 cc.

CASE V. Mr. R. J. R. (213156), a machinist of fifty-four, consulted Dr. Thomas Addis (to whom we are indebted for much of the following) on November 4, 1941, because of edema for two months.

No familial hypersensitiveness was recorded. The patient suffered typhoid fever in 1931. In 1932 he had five days of hematuria, dysuria and nocturia; these disappeared after a tooth was extracted. In 1945 there was an upper respiratory infection complicated by dental abscesses and cervical adenitis; the remaining teeth were removed.

He remained in good health until severe poison oak dermatitis occurred on September 15, 1941, with large vesicles and bullae. Three days later he became edematous and remained so after the skin healed. He felt well but for

dyspnea on effort, attributed to the grossly swollen legs.

Examination showed an obese, pale man with massive generalized edema, ascites and slight hydrothorax. The optic fundi were normal and the radial arteries were thick. The heart was normal. Arterial pressure was 165/95 to 140/90 mm. Hg. The skin was normal and there was no fever.

The volume of packed erythrocytes in the blood was 93 per cent of normal. The serum protein concentration was 4.2 Gm./100 cc., the concentration of urea in the blood was 61.5 mg./100 cc. Seven urinalyses in the next two months showed: 324–512 cc. per twenty-four hours, with specific gravities of 1.035 to 1.024. The rates of proteinuria were 6.6–16.3 Gm. per twenty-four hours, and in that interval the sediment contained 6–40 million erythrocytes, 18–81 million leukocytes and renal tubular cells including oval fat bodies and 6.4–48.6 million casts (chiefly hyaline with fat droplets, none of red blood cells).

Angina pectoris appeared later in November. An electrocardiogram showed left axis deviation, low voltage of the QRS complex and T waves, and a Q wave in lead III. A roentgenogram revealed small amounts of pleural fluid bilaterally and a heart normal in size. A gallop sound was heard inconstantly. Digitalis was added to treatment with nitroglycerine, vitamins and diet. Abdominal paracentesis yielded some 4 L. of pseudochylous fluid.

He entered Lane Hospital in May, 1942. Anasarca was still present. There were no additional physical findings. Arterial pressure was 140/90 mm. Hg. The concentration of hemoglobin was 13.8 Gm./100 cc., and there were 4,380,000 erythrocytes and 6,900 leukocytes (normal differential count, 1 per cent eosinophiles) per cu. mm. Urinary findings were unchanged. The lipemic serum contained 397 mg. of cholesterol and 3.0 Gm. of protein per 100 cc. The Wassermann reaction was negative. The electrocardiogram showed no change. Three infusions of plasma (250 cc.) were followed by a loss of only 5.5 Kg. in two weeks; the third produced orthopnea.

Without much change he returned to the hospital in July, 1942. The concentration of urea in the blood was 66 mg./100 cc., that of protein in the serum 4.0 Gm./100 cc. Urinary findings were similar to those given above. An infusion of plasma was scarcely completed when he suffered severe and continuing substernal

pain; the electrocardiogram showed changes compatible with myocardial infarction. He died within an hour; permission for necropsy could not be obtained.

CASE VI. Miss M. H. (E55127), a clerical worker nineteen years of age, entered Stanford University Hospital October 18, 1946, because of "kidney trouble."

The father had hay fever so badly that he had to move his family, unfortunately to an area in which poison oak abounds. There were no other members with hypersensitive states.

In childhood the patient had measles, mumps and impetigo; the last occurred again in January, 1946. She often had to leave school because of severe urticaria, perhaps related to strawberries and tomatoes. Hay fever occurred once but not eczema nor asthma.

Extensive dermatitis of poison oak appeared almost annually between 1938 and 1944, occasionally enforcing rest in bed for periods up to five weeks at a time. A commercial preparation of poison oak was taken by mouth fairly steadily since 1944 and may have prevented dermatitis at least for a time.

In January, 1945, the ankles and calves became swollen, the last previous bout of poison oak having ended in October, 1944. In February the eyelids also swelled; a blood count was said to have been normal then and the urine not unusual in appearance, but it was not analyzed and the arterial pressure not determined. After another month the edema disappeared, only to return eight to ten times since at intervals of a few months and for a few weeks at a time. The urine was never bloody and was examined several times with negative results while edema was present.

In late July, 1946, poison oak again caused dermatitis but this was not severe. While it was healing, with only a few lesions on the arms, swelling of the eyelids and ankles appeared on August 24th and there were headaches. Edema lasted only a week. No urinary abnormalities were noted but there was no analysis. Symptoms interpreted as "flu" very late in August were followed by a slightly productive cough. By September 10th there was a low grade fever. Hospitalized elsewhere September 23 to 25th, her temperature was reported as 39°C. and her throat reddened but nothing was said of cough and urine. Penicillin was given with subsequent relief of chills and fever. Frontal headaches continued and right lumbar backache commenced at about this time.

On October 6th edema returned and was severe two days later when the urine became brown without oliguria and was found to contain protein, erythrocytes and leukocytes; it was further reported that the arterial pressure was 136-140/90 mm. Hg. One wrist ached temporarily but without swelling on October 12th.

Her general appearance was good; she was ambulatory and there was no fever. The eyelids were not swollen and the optic fundi were normal. The tonsils were small and fibrotic. There was no lymphadenopathy. The lungs were clear and the heart and abdomen perfectly normal. The right lumbar region was tender. There was very slight pitting edema of the ankles, none at the sacral region. Arterial pressure was 125/80 mm. Hg. The joints and skin were normal.

The concentration of hemoglobin was 15.7 Gm./100 cc., and the blood contained 5,200,000 erythrocytes and 14,000 leukocytes per cu. mm. Of these, 78 per cent were polymorphonuclear neutrophils, 11 per cent lymphocytes, 4 per cent monocytes and 7 per cent eosinophils (980 per cu. mm.). The sedimentation rate was 23 mm. per hour (Cutler). The blood contained 33 mg./100 cc. of urea, serum cholesterol was 830 mg./100 cc. without visible lipemia, and the serum protein concentrations were globulin 1.4, albumin 2.6 and total 4.0 Gm./100 cc. An electrocardiogram was normal as was a roentgenogram of the chest.

The urine had a pH of 7.0 with specific gravity of 1.015. It measured 1,088 cc. per twenty-four hours, in which period there were excreted 8.8 Gm. of protein, 100,000 casts (hyaline with heavy fatty inclusions; in several examinations, only one cast thought to be a red blood cell cast was seen), 450,000,000 erythrocytes, 150,000,000 leukocytes and renal tubular epithelial cells exclusive of 12,000,000 oval fat bodies.

Heterophile antibodies, entirely (98 per cent) absorbed by guinea pig kidney but not at all by heated ox erythrocytes (Dr. Sidney Raffel) agglutinated sheep cells in serum dilutions up to 128, while hemolysis of sheep cells took place in dilutions of 128 to 1024. Antistreptolysin titer was 12 units per cc., the cold agglutinin titer 1:4. There were no agglutinins against *E. typhosus* H and O, *S. paratyphosa* A, *S. Schottmülleri*, *Br. abortus*, or Pr. OX2, HX2 and OXK. Agglutination against Pr. OX19 was negative in the tube, positive 1:40 on the slide. The blood Wassermann reaction was

negative. The patient belonged to blood group O,Rh₁.

Management consisted of a diet containing a minimum amount of salt, 40 Gm. of protein and sufficient calories to maintain body weight. She was dismissed from the hospital October

five times, the last episode two years previously. His general health had been good.

The dermatitis of poison oak appeared on November 30, 1946. The lesions were confined to the ankles and were thought to have been infected secondarily after scratching. They

TABLE II
FINDINGS IN CASE VI

Date	Rate of Excretion in Urine per Twenty-four Hours					Serum						
	Protein (Gm.)	Casts (Thousands)	Red Blood Cells (Millions)	White and Epithelial Cells (Millions)	Oval Fat Bodies (Millions)	Lipemia	Cholesterol (Mg./100 cc.)	Proteins (Gm./100 cc.)		Titer		
								Total	Albumin	Anti-streptolysin (Units/cc.)	Agglutinins	Hemolysins
October, 18, 1946.....	8.8	100	450	150	12	0	830	3.98	2.56	12		
October 21, 1946.....	8.4	60	300	120	20	128	512
November, 16, 1946.....	7.2	400	45	120	+	++	630	4.65	3.23			
December, 14, 1946.....	7.2	100	100	30	0	++	...	4.55	2.73	12	64	128
February 8, 1947.....	5.6	100	150	50	+							
March 29, 1947	4.8	0	450	225	8	+	455	4.80	...	12	128	1024
May 29, 1947..	4.0	0	150	220	0	±	430	5.35	3.10	12	40	160
September, 2, 1947.....	4.2	0	225	15	0	..	400	5.45	3.80	12	128	256

25th. By December 14, 1946, the edema had gone and the back seldom ached. In the next three months there were many febrile episodes, including those associated with acute frontal sinusitis and lobar pneumonia. It was not possible to make bacteriologic examinations but the antistreptolysin titer did not rise. Neither gross edema nor hematuria recurred but the intensity of the renal lesion increased. Further findings are given in Table II. Proteinuria has now persisted for fifteen months; the arterial pressure has averaged 130/85 mm. Hg.

CASE VII. A. H. (261081), a schoolboy thirteen years of age, entered Lane Hospital February 25, 1947, because of "blood in the urine" for six weeks.

His father had hay fever and a sister had urticaria. The patient had had severe hay fever. He suffered the dermatitis of poison oak four or

seemed to be clearing, but about December 18th the ankles became covered with moist, dark lesions. Lymphangitis and inguinal lymphadenitis were found and raised erythematous lesions appeared on the forearms. He entered another hospital on December 22nd. There was a low fever (to 38°C.). The urine was normal. Penicillin was started that day. Two days later he had an urticaria-like eruption with vomiting and abdominal discomfort. The lesions promptly disappeared and the infection was pronounced healed.

On December 29, 1946, two days after stopping penicillin and dismissal from the hospital, coffee-colored urine appeared and red blood cells were found in the sediment. The eyelids were puffy. Both flanks ached for a few days. The throat was not sore at any recent time. The urinary abnormalities persisted and he was

referred to Dr. Thomas Addis who advised hospitalization.

Upon examination he appeared well. There was no fever. Arterial pressure ranged from 125/80 to 115/75 mm. Hg. The optic fundi were normal. The tonsils were large and contained pus in the crypts, and there were a few very small, non-tender cervical lymph nodes. The heart was not remarkable but for a moderate systolic blowing murmur at the apex. There was no edema. There were many healed areas of discoloration over both ankles and legs.

The concentration of hemoglobin was 12.5 Gm./100 cc., and the blood contained 4,950,000 erythrocytes and 7,000 leukocytes per cu. mm. Of these there were 63 per cent polymorphonuclear neutrophils, 24 per cent lymphocytes, 12 per cent monocytes and 1 per cent eosinophils. The corrected sedimentation rate was 8 mm. per hour. The concentration of protein in the serum was 5.0 Gm./100 cc. of which 3.2 was albumin and 1.8 globulin. The concentration of cholesterol in the serum was 239 mg./100 cc.; that of urea in the blood was 32.0 mg. and that of creatinine in the serum was 1.37 mg./100 cc. Of phenolsulphonphthalein injected intravenously, 65 per cent was excreted in two hours. An electrocardiogram and roentgenogram of the chest were normal. The circulation time (decholin) was 14 seconds, venous pressure 10.5 cm. Culture of the tonsils revealed a heavy growth of group A hemolytic streptococci; the antistreptolysin titer was 166 units per cc. on both February 25th and March 29th but fell to 100 units per cc. on April 26, 1947. The serum agglutinated sheep cells in a dilution of 1:14.

On February 20th the urine contained 5.7 Gm. of protein and 3,840 million erythrocytes per twenty-four hours, rare granular casts (red blood cell casts were found later) and 240 million white blood and renal epithelial cells. On April 26th after five weeks of rest in bed and a diet low in protein, the urine for twenty-four hours contained only 0.06 Gm. of protein, 210,000,000 erythrocytes and 30,000,000 white blood and renal epithelial cells. Oval fat bodies were not observed.

COMMENTS

Diagnoses. Case I was regarded primarily as one of tubular degeneration with necrosis and anuria, not unlike the "lower nephron nephrosis" syndrome.² In Cases II to V the nephrotic syndrome was prominent. Cases II, III and IV were thought to be

examples of pure lipoid nephrosis; chronic glomerular nephritis was considered present in Case V. Cases VI and VII seemed to be instances of the initial stage of glomerular nephritis; there was a prominent component of tubular degeneration in Case VI as well as a suggestion of periarteritis nodosa (myalgia and arthralgia). In six of the seven cases tubular degeneration or the nephrotic syndrome were present.

It may be noted that the renal complications became obvious in from three days to two months after the onset of dermatitis, usually in one to four weeks. In three patients manifestations of renal disease occurred coincident with the period of recovery from dermatitis.

Other Cases. In addition to these patients, we have heard undocumented reports of four instances of "nephrosis" with one death in some 3,000 to 4,000 soldiers hospitalized for poison oak dermatitis; further details were not available. A syndrome not unlike that of Case I occurred in a man while severe dermatitis of poison ivy was healing;³ it was attributed to injections of a mercurial diuretic given for congestive heart failure and to acute glomerular nephritis. According to the protocol, oliguria and edema appeared before the first injection of the mercurial and about a week after the more or less simultaneous subsidence of the dermatitis and stopping of digitalis; hematuria was microscopic only. An instance of what appeared to be ordinary glomerular nephritis⁴ followed infected dermatitis venenata (sumae⁵). Finally, a case regarded as one of periarteritis nodosa subsequent to poison oak has been described.¹

Coincidence and Infection. In the patients just described, renal complications, especially with tubular degeneration, appeared in close temporal relationship to the healing of poison oak dermatitis. It is recognized that this by no means establishes an etiologic relationship; in Cases IV and V particularly there are no clear past histories of dermatitis and one may be dealing only with coincidence. It is even possible that the occurrences in all of these patients are merely a series of coincidences; satisfactory

data are not available on the incidence of poison oak dermatitis and renal lesions and the problem has not been approached by statistical methods.

Dermatitis of any sort may lead to secondary infection; perhaps it is this factor which is responsible for the subsequent renal involvement. In Case vi there was a suggestion of infection not of the skin but of the respiratory tract; repeated determinations over a period of eleven months showed the antistreptolysin titer to remain at 12 units per cc., but similar low levels have been found even after streptococcal infections in some patients with the nephrotic syndrome.^{5,6,7} In Case vii the skin was infected with an unknown organism, and many hemolytic streptococci of group A were recovered from the tonsils in the absence of sore throat. The antistreptolysin titer was 166 units per cc. on each of two occasions one month apart (similar or higher levels occur in 24 per cent of individuals before and in 77 per cent after a hemolytic streptococcus infection⁸); the fall in titer to 100 units per cc. after one more month is in favor of a streptococcal infection.

It is certainly noteworthy and perhaps significant that in this series of patients gross hematuria and red blood cell casts were found only in the two cases with suspected or definite infection. As noted, a patient similar to the one in Case vii has been reported⁴ as an instance of glomerular nephritis following dermatitis venenata (sumac?) with secondary, unidentified infection of the skin and streptococci in the throat; the antistreptolysin titer was not determined. It seems quite likely that under these conditions the dermatitis of poison oak or related species is not primarily responsible for the ensuing nephritis; it then merely serves as a portal of entry for the hemolytic streptococcus.

TOXIC PRINCIPLE OF POISON OAK AND RELATED PLANTS

Others have well reviewed the chemical and immunologic evidence for the identity of the toxic substance found in poison oak, poison ivy and sumac in this country, in

the Japanese lac tree and perhaps in the mango.⁹⁻¹³ This agent appears to be urushiol, also known as lobinol and toxicodendrol, a catechol compound (other similar compounds may be present) with an average of two double bonds in a hydrocarbon side chain. The molecule has the properties of general toxicity and ability to induce sensitization, at least of the skin.

Direct Toxic and Nephrotoxic Effects. Older literature contains a few references, poorly documented, to severe systemic reactions and death after exposure to rhus. These occurred as results of eating the fruit,¹⁴ chewing the leaves,¹⁵ drinking decoctions^{16,17} or of dermatitis upon contact.^{18,19,20} The prophylactic or therapeutic employment of modern preparations has also been followed by severe reactions.^{21,22} Although local and generalized edema is frequently mentioned by the authors just cited, the urine was generally normal upon the few occasions when it was examined. McNair, however, found proteinuria in one-third of his patients hospitalized with severe dermatitis.^{23,24} His one case of "acute nephritis" is not convincing and there was no mention of any continuing renal lesion; the findings probably represented the proteinuria common in acute illness, particularly in the presence of fever. More recently, proteinuria was not found in a group²⁵ similar to that studied by McNair.

Only four reports have been found pertaining to renal changes after administration of the toxic principle to animals. The most specific claimed that "the irritant properties of toxicodendrol were most marked on the kidneys, producing nephritis and conspicuous fatty degeneration of this organ";²⁶ anuria occurred, followed by the appearance of protein, blood cells and renal epithelium in the urine. Poorly described renal changes were found by two other observers^{27,28} but not by another.²⁹

Although the foregoing observations suggest that there is literally more to poison oak dermatitis than meets the eye, they are completely inadequate as an explanation of events in these patients. If renal involvement had been the immediate result of any

directly acting nephrotoxin, one might have expected its appearance at the height of the dermatitis rather than at or after the stage of recovery; moreover, chronic renal lesions would not be likely.

Hypersensitive State and Poison Oak. Such considerations lead to the proposition that the renal lesions following poison oak in these patients may have been the result of sensitization. All but two patients were known to have suffered repeatedly from the dermatitis, often acquired on slight exposure to the plant. Four had sought relief in the use of commercial extracts of poison oak; in two of the three fatal cases (Cases I and III), in a severe case of periarthritis nodosa¹ and possibly in a fatal case after poison ivy³ extracts were unfortunately used in therapeutic attempts.

Upon their first exposure to the plant or its extract neither infants nor adults react with dermatitis.⁹ Some individuals are highly resistant to heavy exposure³⁰ in spite of evidence that strong concentrations have a direct vesicant activity unrelated to sensitization.³¹ Most workers, however, agree that poison oak (ivy, sumac) dermatitis is a sensitization phenomenon.⁹ The associated chemical and experimental problems continue to receive attention^{9-13, 32, 33, 34} more than a decade after the demonstration that guinea pigs could be sensitized to poison ivy.^{35, 36}

Some immunologic aspects of the sensitization induced by exposure to poison oak have recently been reviewed;⁹ it appears to be similar to cutaneous sensitization induced by other plants and their extracts or by certain chemicals and metals, but it is thought to differ from that responsible for hay fever or bronchial asthma. Antibodies have not been demonstrated either *in vitro* or by passive transfer. It is not altogether clear whether the gastrointestinal involvement after ingestion of the leaves or their extract¹⁰ represents a direct vesicant activity or sensitization; with this possible exception and ignoring a cough sometimes noted during the dermatitis, the skin seems to be the only tissue in which sensitization has

been reported^{23, 24} but this point has not been studied extensively or recently. Attention should be directed to a single case in which a reaction resembling encephalitis followed ingestion of a tincture of poison ivy,²² a reaction which assumes further interest in the light of modern studies on sensitization in the central nervous system.³⁷

It has recently been shown that the intraperitoneal injection of simple chemical compounds which are skin sensitizers results in the formation of precipitins detectable *in vitro* with a gelatin conjugate of the sensitizer.³⁸ The authors did not work with urushiol but indicated that such a pro-antigenic substance might be metabolized to a derivative (quinone) capable of conjugation with protein and the production of incomplete antibodies. In this connection it may be noted that sensitization of the skin has been produced by intraperitoneal injections of extracts of poison ivy.¹¹

Renal lesions and antibodies to kidney have been demonstrated in animals injected with homologous renal tissue to which bacterial toxins had been added.^{39, 40} This suggests, as pure speculation, that the products of poison oak may also incite antigenicity of renal tissue with consequent formation of autoantibodies.

Heterophile Antibodies. Heterophile antibodies do not appear to have been studied in relation to rhus dermatitis. The Forssman substance so widely distributed in nature^{41, 42, 43} could not be demonstrated by Dr. Sidney Raffel⁴⁴ in a commercial extract of poison oak. The titer of sheep cell antibodies was determined in the sera of four patients in this series. In Case II the titer was only 14 seven years after healing of the renal lesion and eight years after its onset. The same low titer was found in Case VII, with initial glomerular nephritis which was probably the result of streptococcal infection. In Case IV (pure lipoid nephrosis or the nephrotic syndrome with chronic glomerular nephritis) Dr. Sidney Raffel⁴⁴ found sheep cell agglutinins in a titer of 128, hemolysins 64. In Case VI (initial stage of glomerular nephritis with nephrotic

component) he found the titer of agglutinins 64–128, that of hemolysins 128–1024. In Case VI the antibodies were 98 per cent absorbed by guinea pig kidney while they were not absorbed by heated ox erythrocytes in Cases IV, VI, or VII.

Parenthetically, it may be noted here that the titer of sheep cell agglutinins was only 7 in a patient with periarteritis nodosa which followed poison oak,¹ but the determination was not made until seven years after the onset. The titer was only 28 in a patient in whom moderately severe but uncomplicated dermatitis had been caused by an injection of rhus extract. On the other hand, moderate elevations of Forssman type antibodies have been found in the sera of other patients with the nephrotic syndrome.

The significance of the findings is not as yet clear. At the moment the presence of heterophile antibodies in these patients does not appear to be related directly to poison oak or sensitization phenomena⁴¹ but rather to alterations in the serum proteins accompanying the nephrotic syndrome.

Hypersensitive State and the Nephrotic Syndrome. As pointed out earlier, renal tubular degeneration or the nephrotic syndrome were prominent in six of the seven patients (Cases I to VI). The hematuric features of glomerular nephritis were outstanding only in those two patients (Cases VI and VII) in whom complicating infection appeared probable, and in another patient¹ thought to have periarteritis nodosa. Recent publications concerned with the rôle of hypersensitivity in the experimental production of arterial and glomerular lesions^{39,40,45,46} have supported older views on the pathogenesis of periarteritis nodosa and glomerular nephritis.

Many authors have commented on the similarities between serum sickness and certain features of the initial stage of glomerular nephritis. However, relationships between the hypersensitive state and the nephrotic syndrome in general or pure lipoid nephrosis in particular do not appear to have been stressed. This type of

syndrome is generally attributed more or less vaguely to infection; in fact, it is not altogether clear whether pure lipoid nephrosis is primarily a metabolic or a renal disorder. Consideration of information available in the literature and of clinical observations suggests strongly that hypersensitivity may sometimes play a prominent part in the pathogenesis of the nephrotic syndrome; the evidence bearing on this point cannot well be given here.

SUMMARY AND CONCLUSIONS

In seven patients renal disturbances appeared during or shortly after the stage of recovery from the dermatitis of poison oak.

In one patient the typical initial stage of glomerular nephritis was probably the result of streptococcal infection. Of all the cases this one was least likely related causally to poison oak.

In another there was fatal anuria with tubular degeneration. A somewhat similar case following poison ivy has been reported by others.

In the remaining five cases renal tubular degeneration was also prominent. The nephrotic syndrome appeared in at least four; three of which were thought to be instances of pure lipoid nephrosis.

The available information relative to the toxic and sensitizing activities of poison oak and related plants was reviewed. The possibilities of explaining the findings by coincidence or infection were considered.

It seems possible and even probable that the renal abnormalities in most of these patients were the result of sensitization induced by poison oak. Final proof, of course, is lacking.

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Primary Carcinoma of the Liver*

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SINCE the time of Virchow, primary carcinoma of the liver has been considered rare. During the past eighteen months we have observed five cases in approximately 500 consecutive cases autopsied at the School of Medicine of the University of Alabama. The difficulty in arriving at a reliable diagnosis of this disease has prompted us to discuss only those cases proved at autopsy. The incidence of 1 per cent in our small series is one of the highest recorded occurring in inhabitants of the western world. Counsellor and McIndoe¹ give the incidence of primary carcinoma of the liver in 42,276 autopsies as 0.14 per cent. Fox and Bartels² found this disease in 0.133 per cent of the subjects in 29,215 necropsies. White³ records an incidence of 0.13 per cent in 18,500 autopsies at Guy's Hospital, London. Goldzicher and Bokay⁴ and Fried⁵ report a somewhat higher incidence, 0.3 per cent, the first in a study of 6,000 and the latter in 1,200 autopsies. Strong and Pitts⁶ report a total incidence of 0.61 per cent in 1,967 autopsies in Vancouver, British Columbia. In the latter report, however, there were ten cases of the disease in 139 Chinese patients who came to autopsy, an incidence of 7.19 per cent. Rosenthal⁷ records that in 2,091 autopsies at Cook County Hospital, Chicago, during 1929 to 1935, there were twelve cases of primary carcinoma of the liver, or 0.57 per cent. Rowan and Mallory⁸ report nine in 6,500 autopsies, or 0.13 per cent; Clawson and Cabot⁹ five in 5,100 autopsies, or 0.09 per cent and Torland¹⁰ ten in 6,000 autopsies, or 0.16 per cent. The literature shows the tumor in an average of 0.5 per cent of cases coming to autopsy.

The incidence of primary carcinoma of

the liver has a definite geographic distribution. It is seen more commonly in Asiatic and South African countries. Nagayo¹¹ reports that in Japan primary carcinoma of the liver ranks from third (in males) to sixth (in females) in occurrence of malignant diseases in that country. In China and Korea it also ranks high. Tull¹² reported finding sixteen cases of primary carcinoma of the liver in 1,312 autopsies in Singapore. The prevalence of the disease among Filipinos is demonstrated by the incidence of the disease at the Manila General Hospital as cited by Reed and DeLeon;¹³ of 1,502 cases to malignancies occurring in that hospital, 1910 to 1914 and 1922 to 1926, 950 or 6.32 per cent were primary carcinoma of the liver.

The Orientals, especially the Chinese, have been shown to have a particularly high incidence of this disease. The prevalence of animal parasite infestation, especially flukes, with resultant cirrhotic changes in the liver has been proposed as the reason for the high incidence of hepatic cancer among Orientals.

Investigators have been instituting a survey in an attempt to explain why primary liver cancer is one of the leading causes of mortality from malignant diseases in Japan in contrast to findings in other countries. Sasaki and Yeshida¹⁴ were able to induce primary cancer of the liver in mice and rats by adding certain azo dyes, especially butter-yellow, to the diet. The occurrence of this azo dye as a coloring agent in the Japanese diet may possibly be a factor which has contributed to the high incidence of this disease in Japan. Orr¹⁵ working in this country has confirmed these observations. He expressed the opinion that the primary effect of butter-yellow on the

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liver parenchyma is destructive and that the resultant proliferative changes are in the nature of regeneration.

Prates¹⁶ reported a series of eighty-five cases among members of the Bantu race in South Africa. Here also the incidence of parasites in the subjects was extremely high, but the author believed that it was not a significant etiologic factor inasmuch as parasitism exists in most natives throughout the tropics without necessarily being associated with primary carcinoma of the liver. In this race the disease occurs especially among young and healthy individuals and the possibility of a dietary factor as an etiologic agent has been proposed to explain the high incidence of the disease.

INCIDENCE

Age. Primary carcinoma of the liver does not exempt any age although it is rarely found in very young children. One case in the series reported here was of a young male fourteen years of age. Steiner¹⁷ reported a case in a male of four months. The fact that primary carcinoma of the liver is found in the very young has evoked the supposition that perhaps these tumors arise from embryonic rests.

Steiner,¹⁷ in his review of the literature, reported seventy-five proved cases in children up to sixteen years of age. In that series 53.2 per cent of the carcinomas occurred in infants under the age of two years, 68 per cent of whom were males. A high percentage of cases occur between fifty and sixty years of age. Three of the cases reported in this paper were in this latter age group.

Sex. It is the universal opinion that primary carcinoma is more prevalent in males than females. For each female there are six males reported with this condition. Many theories have been advanced in an effort to explain this variation. It may be due to the fact that liver cell carcinomas are more frequently preceded by cirrhosis, which is more common in males whereas bile duct carcinoma, preceded by bile duct infections, is found most often in women.

The fact that cirrhosis of the liver plays an important part and is a predisposing factor in the formation of primary carcinoma of the liver is agreed on by practically all authors on the subject. Cirrhosis was present in three of our five cases. Blumenau¹⁸ studied the autopsy findings in 198 cases with a diagnosis of cirrhosis. He found that 3.5 per cent of those in the series had primary carcinoma of the liver. Rosenthal⁷ found that primary hepatic malignancies occur more frequently in cirrhosis with hemochromatosis than in cirrhosis alone. Yamagiva¹⁹ found cirrhosis in 85 to 100 per cent of hepatomas and in 50 per cent of cholangiomas. Fried⁵ postulates the theory that cirrhosis is a reparatory process arising in response to injury. This process is characterized by hypertrophy and hyperplasia of liver cells, resulting in the formation of multiple adenomatous nodules which are potentially malignant. To further elaborate on this important process Glynn²⁰ described a case in which hyperplasia, adenoma and cancer were all found in the same specimen. The vicarious proliferative process for some unknown reason oversteps the normal and takes on the autonomous character of the new growth. Lynch²¹ in attempting to explain the apparent increase of the disease in recent years suggested that it might be related to a more frequent occurrence of a predisposing disease of the liver of the sort which appears to excite proliferation of liver cells, both parenchymal and duct, in notable degrees. In acute yellow atrophy, following recovery, there is more growth of liver and bile duct epithelium than in true portal cirrhosis. It is on the basis of this difference that healed acute yellow atrophy may predispose more to the production of carcinoma.

CLINICAL MANIFESTATIONS

The clinical features, symptoms and diagnosis of primary carcinoma of the liver vary considerably. A review of the literature shows definitely that there is no uniform clinical course which characterizes this disease. In fact, the diagnosis in the vast

majority of the cases reported in the literature was made at autopsy.

The most commonly observed symptoms and signs in our series of patients were palpable abdominal mass, weight loss, right upper quadrant pain, jaundice and ascites.

Abdominal Mass. A distinct mass was palpated in three of the cases reported herein. In all instances the mass was in the right upper quadrant of the abdomen and easily recognized by its protruding above the surrounding level of the abdominal wall. It was always firm, often irregular and only slightly if at all tender. Splenic enlargement was a fairly constant feature. This latter finding was probably due to the underlying cirrhotic process in which splenomegaly is a common finding. Approximately three-fourths of all the cases reviewed had a definitely perceptible abdominal mass.

Pain. This symptom in primary carcinoma of the liver is rarely severe early in the disease but occurs in the majority of cases as was true in our experience. The location of the pain is usually in the epigastrium or under the right costal margin. It is frequently referred to the back and is generally described as a dull, heavy ache and fairly constant in occurrence. The pain is probably due to the expansile mass with resultant distention of the capsule of the liver. The pain encountered could arise from a number of other conditions and is not characteristic; it is therefore of little value in diagnosis. Wilbur²² reported that 72.5 per cent of his patients had upper abdominal pain.

Gastrointestinal Complaints. This complaint was not a common symptom in the cases reviewed; when present it was usually nondescript in character. No definite symptom complex of this nature has been described in the literature.

Jaundice. Four of our five patients were jaundiced either at the time of admission or subsequently in the course of the disease. The degree of jaundice present was variable, with icteric index values of 16 to 33 units. As a rule, jaundice in this disease is

not intense but a fairly constant feature. Ewing²³ found that over one-half of the patients he described had chronic jaundice. Greene²⁴ suggests that the cause of the jaundice may be an obstruction to the outflow of bile caused by the intrahepatic tumors or possibly by enlargement of the hilar lymph glands due to metastasis of the tumor growth. Abel²⁵ believes the jaundice to be due to cachexia with resultant entrance into the circulation of toxic products from the malignant growth.

Ascites. Ascites was present on admission or developed after admission in three of our patients. The fluid was generally blood-tinged. Pathologic examination of the fluid for malignant cells was unsatisfactory. Sixty-six per cent of the cases described by Ewing²³ had ascites. Other authors found a comparable number. The amount varied from slight amounts not easily detected to large amounts causing marked distention of the abdomen. The presence of ascites may be explained on the basis of a cirrhotic liver inasmuch as the latter condition usually precedes primary carcinoma of the liver.

Weight Loss. In reviewing the literature weight loss was a fairly constant feature, as with our cases. Although the loss of weight was not as evident as is seen in a majority of malignant diseases, it occurred in approximately one-half of the cases reviewed. Four of our five patients complained of weight loss prior to admission to the hospital.

Peripheral Edema. Peripheral edema was not a prominent feature in our cases. Plasma protein determinations were not made in enough cases to evaluate the importance of a low albumin level as an etiologic factor in the production of edema. The same factors that produce ascites cause peripheral edema of lower extremities; Therefore, it could be expected in a like number of cases. Such is true in case reports of some workers who found that 42.5 per cent had this complication.²⁶

Bleeding. In one of the cases presented massive hemorrhage was the presenting symptom and caused the rapid demise of

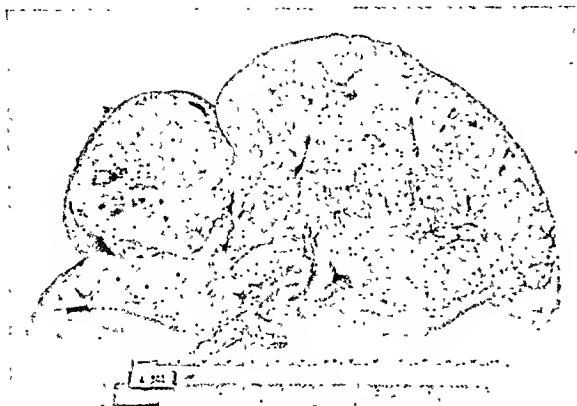


FIG. 1. Primary carcinoma of the liver, liver cell type. Note the many intrahepatic metastases.

the patient. At autopsy this fatal hemorrhage was found to be due to rupture of an esophageal varix. In reviewing the literature hemorrhage was a prominent feature of this disease. Wilbur²² reported recurring epistaxis in four cases, hematemesis and melena in three. Fatal bleeding from esophageal varices occurred twice in this series and fatal epistaxis once. Matthews²⁷ thought that fatal bleeding from varices and from tumors perforating the capsule of the liver was common. In only one of our cases was the prothrombin content of the plasma estimated. A deficiency of this factor occurring from the inability of the liver to utilize vitamin K may play an important part in the production of bleeding tendency in this condition.

Diet. In no case could diet be blamed as an important factor in the production of the disease. Wilbur²² found 22.5 per cent of his patients had used alcohol in considerable quantity but from his data he could not form any opinion as to the importance of this factor in the production of primary carcinoma of the liver.

Blood Picture. There was moderate anemia and the leukocyte count was elevated in more than one-half of the cases. Eosinophilia was present in one subject. The significance of the latter finding is not apparent but it is probably a manifestation of the malignant disease itself. No typical blood picture has been described by authors on this subject; a varied pattern such as we found was seen in most cases.

Roentgenologic Findings. As would be expected this diagnostic method was of little aid. This is to be expected in view of the difficulty of visualizing changes other than those in the size of the liver. Plates showing elevation of the right dome of the diaphragm would be suggestive of this disease process.

Stools. This laboratory procedure failed to reveal any evidence of parasitism in two patients. This finding should be of negative value in diagnosis inasmuch as parasitic infection of the liver could present a very similar picture.

Liver Function Tests. The liver function tests as a rule were disappointing as a method of diagnosis of primary carcinoma of the liver. Damage must be extensive before any appreciable change can be detected in the function tests.

In every case the course of the disease was short. Once symptoms developed to the point that an abdominal mass is palpable and there is jaundice and ascites the course is generally rapidly downhill. Moderate elevation of temperature was seen in most of our patients in the terminal stage. Boyd²⁸ states that fever is present in 10 per cent of the cases and attributes this to marked necrosis found in cases with massive involvement of the liver.

PATHOLOGIC FINDINGS

Primary carcinoma of the liver is classified according to the most likely origin of the malignant cells. The liver cell type of primary carcinoma of the liver is composed of chords, strands and sheets of large, polygonal cells with pinkish cytoplasm and large vesicular nuclei. (Fig. 2.) These cells resemble liver cells and are capable of producing bile both in the primary tumor and in the tumor metastases. This type is the most common primary carcinoma of the liver. Wilbur²² reported an incidence of approximately 92 per cent liver cell carcinomas in his review of forty-nine adult cases. Steiner¹⁷ reported fifty-two liver cell carcinomas, three bile duct carcinomas and twenty-two undifferentiated carcinomas in his report of seventy-seven primary car-

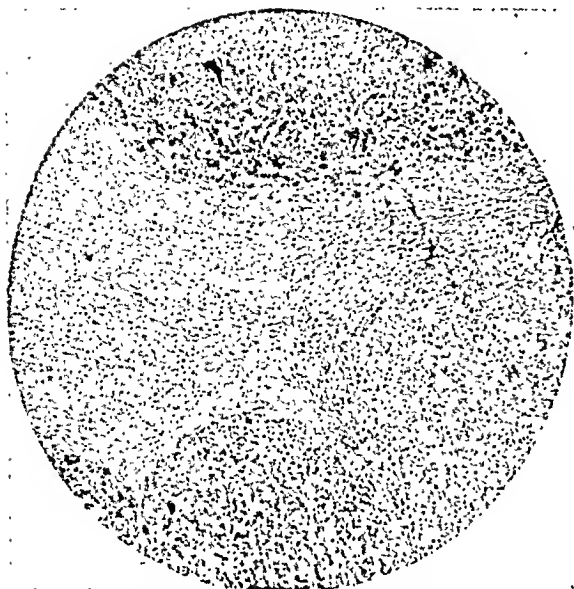


FIG. 2. Liver cell carcinoma. The liver tissue is seen here surrounded by carcinoma; no cirrhosis is present.

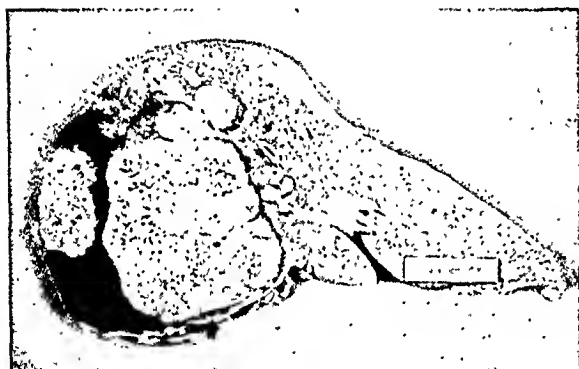


FIG. 3. Primary carcinoma of the liver, bile duct type.

cinomas of the liver in children under the age of sixteen. The bile duct carcinoma arises from the intrahepatic bile ducts. It assumes the appearance of an adenocarcinoma and has a tendency to form tubules and atypical alveolar apices. (Fig. 4.) In this type of carcinoma there is no secretion of bile. The cytoplasm of the cells is lighter staining and more basophilic. The nuclei are hyperchromatic. The stroma in the bile duct carcinoma is made up of connective tissue and tiny capillaries.

Primary carcinomas of the liver not infrequently show both liver cell carcinoma and bile duct carcinoma in the same tumor. This may be classified in a third group, mixed carcinoma. This, however, is the rarest type.

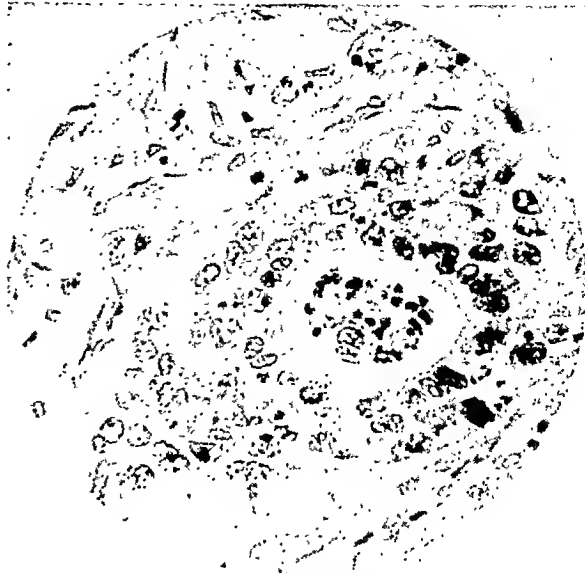


FIG. 4. Bile duct type primary carcinoma of the liver. Note the atypical bile duct formation. Cirrhotic liver is seen above and below the carcinoma.

Three of the carcinomas reported here were of the liver cell type. (Fig. 1.) The other two were bile duct carcinomas. (Fig. 3.)

Although there is some disagreement regarding the development of primary carcinoma of the liver, the generally accepted theory is that they have a unicentric origin. This theory maintains that the multiple nodules of tumor tissue within the liver represent intrahepatic metastasis. A much smaller group believe primary carcinomas of the liver have a multicentric origin.

Intrahepatic metastases are very frequent in primary carcinoma of the liver. This is particularly true in the liver cell type. Extrahepatic metastases are infrequent. Steiner¹⁷ in his review of primary carcinoma of the liver in children found that extrahepatic metastasis occurred in 27.2 per cent of the seventy-seven cases considered. Herxheimer¹⁰ lists metastasis in the following diminishing order of frequency: Lungs and pleura, lymph nodes, bones, epidural space and spinal cord. Uncommon sites are the peritoneum, adrenal, stomach, heart and spleen. Metastasis to the kidney, brain, pancreas and prostate are reported. Mallory²⁹ speaks of the tumor as one which is

likely to metastasis to bone. Liber and Brown³⁰ review the various reports of splenic metastasis and conclude that although many tumor cells are seen in the spleen very few true metastases are found there. As observed by Wilbur²² the multiplicity of intrahepatic metastasis and the sparsity of extrahepatic metastasis suggest a very "individualized" tumor.

Liver cell carcinoma sometimes invades the vena cava. Gregory³¹ reviews twelve incidences of tumor thrombosis of the inferior vena cava. The thrombosis has been known to go into the right auricle as well. Obstruction of the portal vein giving splenomegaly is not uncommon in these tumors.

PRIMARY CARCINOMA OF THE LIVER

Case No.	Type	Metastasis	Cirrhosis
1	Liver cell	Lymph nodes	Absent
2	Bile duct	Lymph nodes	Absent
3	Liver cell	Heart	Present
4	Bile duct	Lungs	Present
5	Liver cell	None	Present

Three of the tumors reported here are metastasized. Two had metastasized to the lymph nodes at the hilus of the liver. One of these had metastasized to the right auricle of the heart as well. In a third metastasis was found in the lungs.

Wilbur²² reports that three of their forty-nine patients showed enlarged livers. There was an enlargement of the liver in each of our five patients. This varied from an increase of 50 per cent to an increase of 200 per cent in weight.

CASE REPORTS

CASE 1. (Unit No. 32387). A male aged fourteen years was admitted to the hospital because of a painful prominent mass in the right upper quadrant. The present illness dated from four months previous to admission. On examination a large mass was found occupying the entire right upper quadrant extending into the epigastrium. A fluid wave was elicited in

the abdomen. Laboratory studies revealed the number of erythrocytes to be 3,900,000 per cu. mm.; hemoglobin was 71 per cent (Sahli); leukocyte count 9,750 with 12 lymphocytes, 11 monocytes, 69 segmented forms, 6 basophiles; the icterus index was 22; the van den Bergh reaction was positive direct and indirect 0.8 mg.; cephalin flocculation test was 2 plus in forty-eight hours; prothrombin time was 105 seconds (control 65 seconds); urinalysis showed a trace of albumin with negative reaction for urobilinogen; stool examinations were negative for ova or parasites. Roentgenologic examination was inconclusive.

The patient was acutely ill on admission and his course was rapidly downhill. Severe paroxysms of pain, which were present on admission, became progressively worse and more frequent toward the end. He expired five days after admission.

At autopsy most of the liver substance was replaced by tumor tissue. (Fig. 1.) On microscopic examination this proved to be primary carcinoma of the liver, liver cell type. (Fig. 2.) The only metastases found were in lymph nodes at the hilus. Jaundice was present but there was no cirrhosis. The spleen was enlarged because of the portal obstruction. No ascites was noted at autopsy. The pancreatic ducts were dilated and a few focal areas of recent fat necrosis were present in the peripancreatic fat.

CASE 11. (Unit No. 172680). The patient, a white female aged fifty-six years, came under observation one year prior to the final admission because of a genito-urinary infection which rapidly cleared on treatment. There was a past history of two gallbladder operations in 1937, the first for cholecystectomy and two weeks later for removal of a stone in the common duct. After nine months she was again admitted with upper abdominal pain which had gradually increased in severity. These symptoms were now accompanied by anorexia, weakness and loss of weight. Physical examination at this time was essentially negative. The roentgenologic examination of the upper gastrointestinal tract, using a contrast media, was reported as normal. On this admission the patient ran a low grade fever which subsided by lysis and the patient was discharged three weeks later. After two months she was readmitted with practically the same complaint but on this admission she was markedly emaciated. The physical examination, again, was essentially negative although

there was some tenderness in the right upper quadrant and the liver was palpable. The liver border was smooth and non-tender. There was no ascites. There was a low grade fever (100°F.). Laboratory studies revealed the number of erythrocytes to be 3,600,000 per cu. mm.; hemoglobin, 61 per cent (Sahli); leukocyte count, 34,000 with 78 segmented forms, 18 lymphocytes, 4 monocytes; urinalysis showed a trace of albumin; stool examination was negative for bile; Kahn serologic test for syphilis was negative.

The patient complained of constant abdominal pain and was nauseated. An exploratory laparotomy was performed on the thirty-first hospital day. About 350 cc. of dark red peritoneal fluid was removed from the abdominal cavity. There was a large space-occupying mass in the right upper quadrant involving the liver. A biopsy was performed. The postoperative course was stormy and the patient expired five days later.

The pathologic diagnosis from the biopsy was carcinoma, type undetermined. At autopsy the carcinoma was seen to be primary in the liver probably arising from a bile duct in the liver substance. The tumor involved chiefly the right lobe of the liver. It had metastasized into lymph nodes at the hilus of the liver as well as to the right auricle of the heart. There was ascites but no cirrhosis.

Death was due to acute purulent peritonitis.

CASE III. (Unit No. 10786.) This seventy-two year old colored male was admitted with the chief complaint of swelling of his abdomen and feet of three weeks' duration. He had been previously treated with digitalis for congestive heart failure and discharged as improved. On this admission his abdomen was markedly distended and was causing respiratory embarrassment. There was a definite fluid wave and shifting dullness. The feet and legs showed a 4 plus pitting edema. A paracentesis was performed and 2,800 cc. of straw-colored fluid was removed. Specific gravity of this fluid was 1.008. Pathologic examination of the fluid for tumor cells was unsatisfactory. The red blood cell count was 3,770,000 with 78 per cent hemoglobin (Sahli). The leukocyte count was 8,000 with 85 per cent segmented forms. The urine was positive for bile; the icterus index was 33 units; van den Bergh reaction was positive direct and the indirect was greater than 8 mg.; the cephalin flocculation test was 4 plus in

forty-eight hours. Roentgenologic examination of the lung fields showed some round, soft, well defined infiltration throughout both lung fields.

The patient expired eight days after admission. A primary liver cell carcinoma which had developed in a cirrhotic liver and metastasized to the lungs was found at autopsy. The liver-like cells constituting the tumor were growing in broad sheets. Many of the bile canaliculi and small bile ducts were dilated, probably due to obstruction of these ducts by tumor nodules. Bile casts were found in the kidney tubules. The body was mildly jaundiced. There was marked splenomegaly. Three L. of ascitic fluid were found in the peritoneal cavity.

The only other significant finding was a mild, left cardiac hypertrophy.

CASE IV. (Unit No. 27636.) A colored male sixty-one years of age was admitted to the hospital with the chief complaint of massive gastric hemorrhage that had begun approximately at 9 A.M. on the day of admission. Two days previous to onset of hemorrhage he had noted that his stools had been tarry. Two months before his admission to the hospital he had complained of generalized weakness. On examination the sclera showed an icteric tint; the abdomen had a definite fluid wave and shifting dullness. A mass that was continuous with the liver margin could be felt in the right epigastrium. The mass was hard, 2 to 3 cm. in diameter, nodular and non-tender. There was splenomegaly. A diagnosis of primary carcinoma of the liver, superimposed on cirrhosis, was made. No laboratory or roentgenologic examinations were recorded. The patient had repeated bouts of vomiting bright-red blood and expired twelve hours later.

At autopsy a primary adenocarcinoma of the liver was found associated with an old cirrhosis of the liver. The secondary effects associated with the cirrhosis were prominent in the form of splenomegaly, esophageal varices and calcific sclerosis of splenic veins. In fact, it seems that the fatal hemorrhage occurred from a ruptured esophageal varix. The carcinoma had not metastasized.

There was cholangitis together with a few small hepatic abscesses. Other findings were a small amount of lobular pneumonia, benign prostatic hypertrophy, and calcification of the mitral valve ring.

CASE V. (Unit No. 12027). A forty-nine year old colored male entered the hospital

complaining of pain in right upper quadrant of four weeks' duration. The pain had steadily increased in severity and occasionally radiated to the right shoulder. There had been a weight loss of 50 pounds and a gradual increasing weakness. On examination the sclera appeared slightly icteric. There was a protuberant mass in the abdomen that was palpable 10 cm. below the right costal margin. The mass was described as smooth and firm and continuous with the edge of the liver. As seen from a lateral view the mass extended above the surrounding level of the abdominal wall. There was a definite fluid wave. Laboratory examination showed the erythrocyte count to be 4,390,000 with 80 per cent hemoglobin (Sahli); total leukocyte count 7,800 with a normal differential ratio; icterus index was 16 units; cephalin flocculation test 3+ (forty-eight hour reading); sickle cell preparation negative; examination of feces for occult blood, ova and parasites was negative. Roentgenologic examination showed an elevated fixed right diaphragm; the gallbladder responded to the dye; contrast media showed no intrinsic lesion in the gastrointestinal tract.

On the twenty-first hospital day an exploratory laparotomy was performed under local anesthesia. The peritoneal cavity was found to contain a moderate amount of blood-tinged ascitic fluid. The liver was seen to be enlarged, nodular, firm and dark red in color. A biopsy was performed. The postoperative course was stormy. The patient expired on the eighth postoperative day.

At autopsy (limited to the abdominal cavity) a primary liver cell carcinoma was found. There was also a diffuse nodular cirrhosis with splenomegaly, jaundice and ascites. No metastases of the tumor were demonstrated.

There was an acute purulent peritonitis which was the probable immediate cause of death.

SUMMARY AND CONCLUSIONS

Five cases of primary carcinoma of the liver have been presented. All cases were proved at autopsy. The recent incidence of primary carcinoma of the liver in our hospital, 1 per cent, is one of the highest reported from the western world. Three of the cases were of the liver cell and two of the bile duct type. Cirrhosis was present in three of the five cases.

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Primary Carcinoma of the Liver*

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THE rarity of primary carcinoma of the liver in Europe and North America and the difficulty in establishing diagnostic criteria for this condition have prompted us to make a study of the various patients seen at autopsy and operation at the Jewish Hospital of Brooklyn.

TABLE I

Spatt and Grayzel	Pack and Lefevre ¹¹	Wilbur et al. ¹⁵	Gnass ⁸	Loesch ¹⁹	Gustafson ⁸	Charache ⁵
0.23%	0.17%	0.44%	0.14%	0.46%	0.26%	0.56%

A series of seventeen cases of primary carcinoma of the liver is presented of which eleven have come to autopsy. Of a total of 4,731 postmortem studies done at this hospital up to July, 1946 eleven autopsied cases of primary carcinoma of the liver were seen (0.23 per cent). For comparison with the incidence in other series see Table I.

It is well known that the incidence of this lesion is much higher among Asiatics than it is among those of Europe and America. For example, Berman² gave the percentage of primary carcinoma of the liver in all autopsies as 1.3 per cent for Javanese, 1.21 per cent for Japanese and 1.2 per cent for the Bantu tribes of Africa.

Of the eleven autopsied cases, nine were adults and two were children. The latter were four months and one year and four months old, respectively. Of the nine adults who came to necropsy, seven (78 per cent) had accompanying portal cirrhosis in the portion of the liver uninvolved by the tumor. This compares with 54 per cent in the series of Wilbur et al.¹⁵ This latter figure is much lower than is found in most other series, i.e., Loesch⁹ 86 per cent, and

Greene⁷ who, in 386 cases gleaned from the literature, found the percentage of cirrhosis in hepatocellular carcinomas to be 87 per cent. Strong and Pitts¹² found that in ten cases in Chinese people, 100 per cent had cirrhosis of the liver. Tull¹³ stated that cirrhosis was present in the great majority

TABLE II

Location of Metastases	Spatt and Grayzel, Per cent	Wilbur et al.	Loesch	Gustafson	Greene
Lungs.....	67	second most common	second most common	second most common	
Tumor thrombi in veins.....	44	most common	*	
Omentum.....	33				
Bones.....	22				
Regional lymph nodes.....	22	most common site	most common site	most common site
Suprarenal glands.....	22				
Pancreas.....	11				

of cases, especially those of the liver cell type. Brines⁴ stated that a much higher percentage of primary carcinoma of the liver is apparently found in autopsies on patients in whom chronic liver diseases are present. The aforementioned statements and figures indicate that chronic liver disease plays some etiologic rôle in carcinoma of the liver, or that a common etiologic factor may be involved in both conditions. Of the eleven cases which came to necropsy, 9 (82 per cent) showed extrahepatic metastases. (See Table II for the location of metastases and a comparison with other series.)

Extrahepatic metastases occurred in six of seven hepatocellular (86 per cent), in two of three cholangiocellular lesions and in

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one undetermined cellular type. Of the present series of seventeen cases ten (59 per cent) were hepatocellular, five (29 per cent) were cholangiocellular and two (12 per cent) were of undetermined origin. (For comparison with other series see Table III.)

Primary carcinoma of the liver is obviously a disease which preponderantly affects males. There is no significant history of alcohol in our patients to account for the difference in incidence between males and females. The greater incidence in males

TABLE III

	Spatt and Grayzel, Per cent	Wilbur et al., Per cent	Loesch, Per cent	Gustafson, Per cent	Greene	Strong and Pitts, Per cent	Tull
Hepatocellular	59*	92	86	63	"Liver cell carcinoma far outnumbered duct cell carcinomas"	67	"Liver cell type is nearly 3 × as common as the bile duct type"
Cholangiocellular	29	8			
Undetermined	12			

* If the two cases of undetermined type of carcinoma were to be added to the hepatocellular group, the percentage (71 per cent) would more nearly approximate those of most other workers.

TABLE IV

Age	Spatt and Grayzel, Per cent	Wilbur et al.	Loesch	Gustafson	Greene	Upham and Klotz ¹⁴
45-54	27	Most cases between 41 and 70 years fairly well distributed in the three decades between 41 to 70	Highest incidence in fifth, sixth and seventh decades	Greatest incidence 50 to 59 years	Greatest incidence between 40 and 60 years
55-64	46					
65 and over	27					
Average age	60 years	60 years	59.5 years	52.5 years		

The youngest patient in our series was four months old; the oldest was seventy-three years old. There was no significant difference in the ages of the males and females. (See Table IV for comparison with other series.)

The ratio of males to females in the authors' cases was 65 per cent males and 35 per cent females. (For comparative figures see Table V.)

TABLE V

	Spatt and Grayzel	Wilbur et al.	Loesch	Gustafson	Greene
Males (per cent)	65	86	86	85	86
Females (per cent)	35	14	14	15	14

may be at least partially accounted for by the greater frequency of cirrhosis of the liver in males. Certainly, the two conditions, cirrhosis and carcinoma of the liver, occur together very frequently.

CLINICAL DATA

The length of the clinical course in this series varied from one to twelve months with an average of three and three-fourths months. In 86 per cent of the cases it was less than five months. The short clinical course is similar to that found by most other workers in the field. In fact, Upham and Klotz¹⁴ and Morehead¹⁰ maintained that patients with untreated carcinoma of the liver never survive more than four months.

(For the most consistent signs and symptoms see Table VI.)

Thus the signs and symptoms are seen to be non-specific so that this diagnosis is a very difficult one to make clinically. As Boyce and Mcfetridge³ put it, "The clinical

TABLE VI

Signs and Symptoms	Percentage of Cases in Which Signs and Sym- ptoms Were Pres- ent
Rapidly enlarging abdominal mass.	88
Abdominal pain.	82
Sustained temperature of over 100°F.	64
Marked weight loss.	53
Severe anorexia.	47
Nausea and vomiting.	47
Constipation.	47
Icterus.	47
Ascites over 1,000 cc.	35*

* In 50 per cent of these the fluid was bloody.

course is absolutely atypical and diagnosis is rarely made antemortem except in those localities in which the disease is relatively frequent."

The diagnosis was made clinically in the authors' series in only 6 per cent of the cases. The remainder of the patients were diagnosed only after operation or post-mortem examination. The diagnosis made in most of the patients was either "cirrhosis of the liver" or "carcinoma, metastatic, in liver." Difficulty in diagnosis was noted by all the workers in this field except those in South Africa and Asia where the disease occurs fairly frequently. The importance of early diagnosis is perhaps not too great at present since little can be done in the way of treatment. However, some authors^{1,5,14} recommend surgical extirpation of the tumor as a treatment offering some hope. In fact, Charache⁵ mentions one case of a nine-year cure after surgery. On the other hand, surgery is thought to be of doubtful value by others.^{2,7}

LABORATORY DATA

The icterus index varied from 8.4 to 380.4 in nine patients. The average value was 84.1. There were only two values below 10 and there were six values above 40, so that the icterus index was high fairly con-

sistently in this series. In fourteen patients, the blood sugar varied from 73 to 153 mg. per cent. The average value was 108 mg. per cent. Thus it may be seen that there was no significant variation in the blood sugar from the normal in these patients.

TABLE VII*

Case I.	15 per cent dye retained after thirty minutes
Case II.	20 per cent dye retained after thirty minutes
Case III.	30 per cent dye retained after thirty minutes
Case IV.	90 per cent dye retained after thirty minutes

* 5 mg. of dye/Kg. of body weight given.

The alkaline phosphatase value varied from 6.1 mg. per cent to 28.3 mg. per cent (Bodansky units); the average value was 16.9 mg. per cent. Of seven patients in whom this test was recorded, all were above the normal value. In five patients the values were above 19 mg. per cent; in only one of these were there metastases to bone. Therefore, it may be said that the alkaline phosphatase is usually high in primary carcinoma of the liver. The serum protein value varied between 5.7 and 6.9 Gm. per cent so that there was no significant change.

The total blood cholesterol in seven patients varied from 159 mg. per cent to 352 mg. per cent. Normal values in this institution are 150 to 280 mg. per cent. The total cholesterol values were above the upper limits of normal in only two cases. The percentage of free cholesterol was higher than the upper limits of normal in three patients, the extreme being 85.4 per cent (normal 22 to 28 per cent). Thus the cholesterol values were not significant in this group of patients. The cephalin flocculation test was recorded in six patients and varied from negative to 3+. It did not yield consistent results in this series. In four cases the bromsulphalein test was done, with results as seen in Table VII.

Thus these test values consistently indicated liver damage. Their significance is limited only by the small number of bromsulphalein tests done. In thirteen patients in whom the red blood cell count was recorded the extremes were 1,450,000 and 4,800,000 and the average was 3,700,000. Severe anemia did not occur frequently.

SUMMARY AND CONCLUSIONS

1. A series of seventeen cases of primary carcinoma of the liver has been studied and the literature reviewed.

2. The rarity of the lesion in this area was confirmed (0.23 per cent of all autopsies).

3. There was some indication that cirrhosis of the liver plays a rôle in the etiology of this disease, or that some etiologic factor is common to both.

4. Extrahepatic metastases were present in 82 per cent of the patients.

5. Hepatocellular lesions far outnumbered those of cholangiocellular origin.

6. The age incidence varied from four months to seventy-three years, almost one-half the cases occurring between fifty-five to sixty-four years.

7. Males predominated over females (2:1).

8. The length of the clinical course was short, averaging three and three-fourths months.

9. The most consistent signs and symptoms were (1) rapidly enlarging abdominal mass, (2) abdominal pain, (3) sustained temperature over 100°F., (4) marked weight loss. Anorexia, nausea and vomiting, constipation, icterus and ascites were less frequent.

10. Diagnosis is difficult and infrequently made clinically.

11. The most consistent liver function tests were (1) icterus index, (2) alkaline

phosphatase, (3) bromsulfalein test. The blood sugar, serum protein, cholesterol, cephalin flocculation test and red blood cell counts were not significant.

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So-called Extrarenal Uremia*

A Study of Twenty Cases

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DURING Bright's time and until recently uremia was considered one of the chief syndromes of renal insufficiency brought about by nephritis, obstructive uropathies or some other organic disease of the kidney. The occurrence of uremia in the absence of demonstrable and significant renal lesions, however, is an unexpected event more frequent than it is thought to be and which is often overlooked. This condition was not recognized until the year 1912 when Froin and Marie¹ and Nobécourt, Bidot and Maillet² observed this clinical syndrome in patients suffering with cholera and diarrhea in infancy. Tilston and Comfort³ in 1914 in an investigation of azotemia of non-renal origin gave a more comprehensive description of the disorder.

Since that time, many articles⁴⁻¹⁵ have described extrarenal uremia, and the conditions held responsible for this syndrome have been numerous and varied. Intestinal obstruction, hepatitis, diabetes, myocardial infarction, Addison's disease, shock, burns and hemorrhage are a few conditions often associated with it. But almost any serious illness or injury may be looked upon as a cause of extrarenal uremia. A puzzling question is whether or not, in all of these cases, there is a common factor accountable for the extrarenal uremia. So far there is no satisfactory answer.

Since extrarenal uremia (prerenal uremia, non-renal azotemia) occurs in association with some primary serious disorder, its features may be confused with signs and

symptoms of the original disease. As extrarenal uremia is a clinical syndrome its features are not always the same. However, some of the chief characteristics are uniformly present despite the diverse nature of the primary disorder responsible for it. Dehydration, stupor, azotemia, low blood pressure and a shock-like appearance are practically always found. In some cases alkalosis and hyponatremia are present and in others acidosis and normal chloridemia exist.

Considerable dissatisfaction has arisen over the use of the term extrarenal uremia. Prerenal azotemia and non-renal azotemia have been substituted for it.^{19,25} The chief fault found with the term extrarenal uremia is that it fails to differentiate the azotemias due to obstructive uropathies from the nitrogen retention of metabolic origin. The terms extrarenal uremia and extrarenal azotemia are frequently used interchangeably. This is not quite correct for extrarenal azotemia indicates merely a retention of nitrogenous substances in the blood which depend upon factors operating in the absence of primary renal impairment. Extrarenal uremia, on the other hand, is a symptom complex in which azotemia is always present, but there are other signs and symptoms which characterize it, such as stupor, delirium, twitching and a shock-like appearance. However, use of the term uremia has become fairly well entrenched in the literature and until a more appropriate term becomes established we believe it is wise to adhere to it. It should be kept

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in mind that the term extrarenal uremia indicates that the chief factors responsible for it occur outside of the kidney, such as shock, dehydration and vomiting. Nevertheless, extrarenal uremia which ensues is a result of renal insufficiency even though functional in nature. Regarded in this light the term extrarenal uremia is a misnomer, and the older generation of clinicians may have been correct in holding the opinion that all uremia emanates from disordered kidneys. There is one prominent difference between the common type of genuine uremia and the kind under discussion here: that is the absence of organic changes in the kidney other than those usually found in the kidneys of patients dying from any long illness without disease of the kidney. In the study of eighty-four cases of extrarenal azotemia Bell and Knutson¹⁶ found mild to severe hydropic degeneration of the proximal convoluted tubules in twenty, indicating that tubular injury may have been, in part, or entirely responsible for the uremia. In the remaining sixty-four there were no structural changes in the kidney. As they point out it is difficult to make a sharp differentiation between true extrarenal azotemia and azotemia due to tubular injury. So-called extrarenal uremia is a functional disease of the kidney which is the result of one or more disorders occurring outside of the kidney. It is still necessary, however, to give consideration to the mechanisms which diminish renal function and produce so-called functional or extrarenal uremia.

The purpose of this report is threefold: (1) To present a group of twenty cases illustrating extrarenal uremia and the varied types of primary diseases which may be responsible for it. (2) To emphasize the importance of recognizing this syndrome early because if the proper diagnosis is made rational treatment is followed by gratifying results. (3) To emphasize the need for further investigation of the kidney in extrarenal uremia, with special attention to the tubules and the recent work of Trueta et al.¹⁷

In Table I is a summary of the twenty cases which were selected to illustrate the clinical, chemical and pathologic features of this disorder. The cases are arranged according to the primary disorder considered to be the cause of extrarenal uremia. Cases I to IX resulted from gastrointestinal disorders. Cases X to XIII were associated with hepatitis or some form of liver disease. Cases XIV and XV followed infection and Cases XVI and XVII were examples of vasomotor disturbances associated with heart failure due to coronary artery disease; the brain and peripheral nervous system were involved in Cases XVIII to XX.

In all the patients in the gastrointestinal group there was excessive vomiting, dehydration and pain in the upper abdomen. One patient had marked diarrhea with associated acidosis, six had alkalosis and three had acidosis. There was a previous ulcer history in four of the nine patients and three of the four had suffered perforation. Oliguria and hemoconcentration were present in all nine patients. In three of the nine evidence of tetany was present on first examination. In one patient there were cramps of the hands and feet for two months prior to the onset of symptoms of his last admission. Four of the patients showed symptoms of delirium, stupor or hyperactivity and this we believe constituted evidence of uremia as differentiated from simple azotemia. Six of the nine patients recovered with appropriate treatment which was aimed primarily at restoring the fluid and electrolyte balance as well as correcting mechanical obstructions present by surgical measures. During the course in the hospital one patient (Case IV) showed evidences of some structural damage of the kidney. After death and at autopsy this was borne out by the finding of distinct changes in the tubular epithelium of the proximal and distal convoluted tubules. The epithelial cells were swollen and showed granular dehydration throughout. The glomeruli were intact, and there were arteriosclerotic changes in the medium-sized and smaller

TABLE 1
SUMMARY OF CASES

Case Age Sex	Admit- tance Date	History	Examination	Blood Pres- sure	Urinalysis	Blood Chemistry	Laboratory Data	Treatment	Remarks
i 37 w/m	2/15/46	Ruptured gas- tric ulcer Upper ab- dominal pain Vomiting Weakness Weight loss	T. 97.8°F. P. 76 R. 18 Restless Hiccoughs Dehydrated Abdominal tenderness	140/80	Sp. gr., 1.004 tn 1.012 Alb. 0 Sugar 0 Later: Alb. 2+ R.B.C. occasional W.B.C. oc- casional casts 1 to 2 (hya- line)	N.P.N. 137.8 NaCl 200 CO ₂ 97.0 Sugar 148.2	Addis count R.B.C. 4,906,543 W.B.C. 19,631,258	Penicillin 4,000 cc. glu- cose + saline Gastric aspira- tions up to 900 cc. Gastrojeju- nostomy	Operative findings: Prepyloric cicatrix pro- ducing almost com- plete obstruction Numerous adhesions between liver and first part of duodenum and anterior aspect of pan- creas Discharged, improved
ii 52 w/m	5/10/44	Vomiting 5 mo. Persistent peptic sub- phrenic ab- scess Congenital kidney disease	T. 98.6°F. P. 88 R. 24 Irrational Dehydrated Muscular twitchings Positive Trousseau and Chvostek signs Abdomen rigid with hy- poactive B.S.	140/90	Sp. gr. 1.011 Alb. 3+ R.B.C. 0 W.B.C. many Casts 0	N.P.N. 97.7 NaCl 240 CO ₂ 87.0 Normal on 10th postop- erative day	W.B.C. 17,000 Gastric reten- tion at 4 hr.	Wangensteen suction 4-6,000 L. n/saline Postgastro- enterostomy	Dense adhesions above liver, duodenum and pylorus Discharged as improved 31st hospital day
iii 52 w/m	8/15/42	Epigastric pain Vomiting Cholecystec- tomy for gall- bladder em- pyema 2 yr. prior to entry	T. 100.6°F. P. 100 R. 28 Sluggish Dehydrated Enlarged liver Jaundice	105/65	Sp. gr. 1.016 Alb. 3+ Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0	N.P.N. 104 NaCl 260 CO ₂ 40.0	Cholesterol 132 Icteric Index 45	Wangensteen suction 6,000 cc. parenteral fluids	Expired No postmortem
iv 56 w/m	2/21/42	Nausea 1 mo. Vomiting Repair of per- forated pep- tic ulcer Occasional pain Urinalysis negative on previous admission	T. 96.4°F. P. 118 R. 26 Dehydrated Soft abdomen with marked tenderness Confused Disorientated	105/85	Sp. gr. 1.012 Alb. + Sugar 0 R.B.C. 2 W.B.C. 4 Casts occasional	N.P.N. 226.5 NaCl 340 CO ₂ 78.0	4,000 cc. glucose in saline	Expired 11th day Gastric ulcer Pyloric stenosis Interstitial renal edema and tubular degenera- tion
v 48 w/f	4/23/46	Vomiting Nausea Cramps of hands and toes Previous gas- tric ulcer Oliguria for 5 days	T. 99.8°F. P. 108 R. 12 Weak pulse Respirations shallow Epigastric tenderness Distention	106/70	Sp. gr. 1.010 Alb. 3+ Sugar 0 R.B.C. 5-10 W.B.C. 15-20 Casts 0	N.P.N. 150.8 NaCl 260 CO ₂ 65.5	W.B.C. 8,800 Hgb. 94%	Intravenous calcium glu- conate 5,000 cc. saline intravenously	Improved Discharged 4/27/46
vi 28 w/f	5/19/46	Nausea Vomiting Rectovaginal fistula and abscess Chronic ulcer Colitis Profuse exu- date from distal loop of ileostomy	T. 98°F. P. 140 R. 30 Ileostomy with drain- age of recto- vaginal fistula and abscess Marked ema- ciation Weakness Pallor	110/70	Sp. gr. 1.015 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. occasional Casts 0	N.P.N. 82.5 NaCl 280 CO ₂ 84.8	Sed. rate 32/63 W.B.C. 50,600 Hgb. 95.5%	Plasma Saline Wangensteen suction External heat Blood trans- fusion	Improved after 12 hr.

TABLE I.—(Continued)

Case Age Sex	Admit- tance Date	History	Examination	Blood Pres- sure	Urinalysis	Blood Chemistry	Laboratory Data	Treatment	Remarks
vii 22 w/f	2/4/46	Vomiting Diarrhea Abdominal cramps Irrational	T. 101°r. P. 110 R. 16 Physical findings essentially negative	122/82	Sp. gr. 1.010 Alb. 2+ Sugar 0 R.B.C. oc- casional W.B.C. few Casts occasional Amt. 400-800 a day	N.P.N. 132 NaCl 375 CO ₂ 30 Normal after parenteral saline	Lungs normal Gastro- intestinal series negative W.B.C. 18,500 Blood chn- lesterm 210	Normal saline 3,000/d for 3 days	Recovery in about 2 wk. Stuporous, irritable and partially irrational response with clinical improvement on 3rd day
viii 26 w/f	11/3/46	Vomiting Nausea Nocturia Pregnant 4 mo.	T. 98°f. P. 110 R. 26 Distended small bowel Tender	84/60	Alb. 2+ Sugar 0 W.B.C. oc- casional R.B.C. 0 Oliguria	N.P.N. 125 NaCl 313 CO ₂ 67	Obstructive in duodenum Pregnant 4 mo.	Removal of ob- struction Meckel's diverticulum	Recovery
ix 74 w/f	10/7/45	Epigastric pain Nausea Vomiting	T. 100°f. P. 80 R. 20 Tender abdomen	104/60	Oliguria negative	N.P.N. 157.6 NaCl 360.0 CO ₂ 42.8	Hgb. 88% W.B.C. 10,500 Sed rate 102/110	Wangensteen suction Penicillin Oxygen Plasma Fluids	Expired 19 hr. after admission
x 64 w/m	4/26/46	Weakness Jaundice Ankle edema Abdominal pain Weight loss Anorexia Dysuria Alcoholism	T. 96.4°f. P. 120 R. 26 Confused Dehydrated Hemorrhages of the soft palate Abdomen tense Liver en- larged and tender Jaundice	90/48	Alb. 1+ Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0 Bile +	N.P.N. 200.0 NaCl 440 CO ₂ 52	Kline nega- tive R.B.C. 3.23 W.B.C. 18,650 Hgb. 81% Icteric Index 94.8 Bleeding time pm- ingd over 24 minutes	Antispasmodics Alkalinization Intravenous fluids Vitamin C Sedation Wangensteen suction Anigen Liver extract Synkamin Intraheptol	Expired 4/30/46 Cholemia Hepatitis, non-specific Nephrosis, cholemic and sulfonamide Coronary and renal arteriosclerosis with myocardial fibrosis Cerebral edema with focal encephalo- malacia
xi 28 w/m	1/5/44	Inability to void for 48 hr. Edema Abdomen dis- tended Jaundice	T. 98.8°f. P. 90 R. 20 Enlarged heart Edematous Hydration adequate	124/60	Sp. gr. 1.015 Alb. 3+ Sugar 0 R.B.C. 0 W.B.C. 0 Casts 2+ granular	N.P.N. 95.2 NaCl 400 CO ₂ 27.7	W.B.C. 17,500 Hgb. 15.5% Blood culture negative	Glucose and sodium lactate Intravenous solutions	Expired 1/11/44 Uremia Cirrhosis of the liver Anasarca Congested kidney
xii 28 w/m	9/30/43	Confused Weakness Alcoholism Weight loss	T. 96.4°f. P. 119 R. 23 Irrational Dehydrated Liver enlarged	116/84	Sp. gr. 1.017 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. oc- casional Casts 0 Oliguria	N.P.N. 130 CO ₂ 23.0	Chest x-ray negative Sed. rate rapid	Oxygen 3,000 cc. glu- cose + saline Intravenous cal- cium gluconate	Expired 10/18/43 No postmortem
xiii 54 w/m	4/17/46	Dyspepsia Hematemesis Jaundice	T. 101.2°f. P. 110 R. 30 Liver enlarged 1+ edema of legs	138/70	Sp. gr. 1.021 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 0 Casts few	N.P.N. 41.3 NaCl 302 CO ₂ 38.0	R.B.C. 2,300,000 W.B.C. 5,200 Hgb. 50.5% Examination of lungs negative	Sedation 2,500 cc. Blood trans- fusion 2,000 cc. 5% glucose/d Sodium lactate	Expired 4/22/46 Hepatic portal cirrhosis esophageal varices Icterus Renal congestion
xiv 55 w/f	3/25/44	Vomiting Epigastric pain Weakness Numbness Weight loss Oliguria Thirst	T. 97°f. P. 120 R. 30 Dehydrated	90/60	Sp. gr. 1.014 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 10.20 Casts 0 Oliguria	N.P.N. 88.4 NaCl 586 CO ₂ 27.7 Sugar 286	Sedation Fluids	Expired 3/27/44 Pulmonary tuberculosis Tubercular bronchi- ectasis of left apex Tubercles of left lower lung Tubercular enterocoli- tis Myocardial degenera- tion Cerebral edema

TABLE I.—(Continued)

Case Age Sex	Admit- tance Date	History	Examination	Blood Pres- sure	Urinalysis	Blood Chemistry	Laboratory Data	Treatment	Remarks
xv 61 w/m	10/2/31	Pain in left chest Chills Fever Sweating	T. 102.8°F. P. 120 R. 32 Consolidation of left chest Tachycardia	118/84	Sp. gr. 1.012 Urine nega- tive Later: Alb. 1-2+ R.B.C. 4 W.B.C. 8-10 Casts oc- casional granular	N.P.N. 94 CO ₂ 45	Left hydro- thorax Consolidation of left lung	Aspiration Rib resection with drainage Intravenous fluids	Recovery 2 wk. Oliguria during hospital stay
xvi 51 w/m	5/7/46	Substernal pain Shock Vomiting Dyspnea Alcoholism	T. 100.6°F. P. 120 R. 40 Restless Enlarged liver Cyanosis of lips and nail beds	98/70	Sp. gr. 1.016 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0	N.P.N. 120 NaCl 310 CO ₂ 42	ECG showed myocardial infarction of anterior wall W.B.C. 31,400 Hgb. 101%	Oxygen Pantopan Plasma Atropine Quinidine Whiskey	Expired 4th hospital day No autopsy
xvii 54 w/m	2/28/44	Epigastric pain Nausea Vomiting Tachycardia	T. 97°F. P. 120 R. 26 Auricular fibrillation Epigastric tenderness Irrational	88/62	Sp. gr. 1.012 Alb. 0 Casts few Oliguria	N.P.N. 72 NaCl 273 CO ₂ 78	Hiatus hernia Auricular fibrillation	Intravenous NaCl and glucose 4,000 cc. in- travenously	Full recovery on 10th day
xviii 54 w/m	9/12/45	Vomiting 3 weeks	T. 100°F. P. 90 R. 24 Bitemporal hemianopsia Positive Hoff- mann's sign bilaterally Weakness of right side of face Tongue devi- ated to right	160/ 100	Sp. gr. 1.015 Alb. trace W.B.C. oc- casional R.B.C. 0	N.P.N. 108 NaCl 627 CO ₂ 32	Skull x-ray re- vealed erosion of posterior clinoids	Surgery Intravenous glucose	Azotemia corrected Patient died following surgery Chromophobe ade- noma of pituitary
xix 51 w/f	4/4/46	Psychosis- mania hy- peractivity Semistupor- ous	T. 107.6°F. P. 120 R. 27 Bigeminal pulse Skin cool and moist Cyanotic	Un- ob- tain- able	Sp. gr. 1.008 Alb. + Sugar 0 R.B.C. rare W.B.C. 5-10 Casts rare	N.P.N. 128 NaCl 295 CO ₂ 62	Spinal fluid negative Kline nega- tive	Oxygen Plasma 600 cc. Parenteral glu- cose and saline 3,000 cc.	Lapsed into coma Expired after 20 hr. in hospital
xx 33 c m	3/26/46	Fever Hyperactivity Psychosis Catatonia	T. 101.2°F. P. 130 R. 27 Restless Muttering Frequent bowel move- ments Mucous membranes dehydrated	110/70	Sp. gr. 1.006 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0	N.P.N. 110.8 NaCl 270 CO ₂ 84	Spinal punc- ture negative W.B.C. 15,200 Hgb. 88% X-ray of chest negative	Parenteral fluids Glucose and saline up to 3,000 cc. daily Penicillin	Improved Discharged 4/22/46 No cause for fever found

arteries of the kidney but not of an advanced degree.

The following is an illustrative case of the gastrointestinal group. This patient vomited as the result of pyloric obstruction which developed subsequent to an old perforated

gastric ulcer. It also shows the effectiveness of treatment in this type of case.

CASE REPORTS

CASE I. F. L., a thirty-seven year old white male, was admitted on February 15, 1946. For a

period of three days the patient had severe epigastric pain with marked vomiting, followed by stupor two hours prior to admission. He suffered a ruptured gastric ulcer nine years previously and was operated upon at that time. A few months following this he experienced postprandial pain. During the eleven months prior to the last admission he suffered repeated episodes of vomiting, weight loss and cramping of the hands and feet with marked paresthesia. Consumption of large quantities of baking soda was the only means of relief. Examination on entrance revealed a well developed, undernourished, stuporous white male, with marked pigmentation of the skin. Pulse was 76; respirations, 18; temperature, 97.8°F. and blood pressure 140/80. He was irritable, hiccupped continuously and his tongue was very dry. The sclerae were clear and the fundi were normal. There was a negative Chvostek's sign. Examination of the chest, lungs and heart disclosed no abnormalities. There was an epigastric scar. There were no abdominal masses; the gurgles were normal and no distention or rigidity were found. The entrance impressions were compatible with Addison's disease, drug intoxication or possibly uremia. Laboratory tests showed a non-protein nitrogen of 137.8 mg. per cent and an alkali reserve of 97 volumes per cent. The urinalysis was negative for albumin, sugar and formed elements. The blood disclosed the following: hemoglobin, 97 per cent; white blood cells, 27,550; bands, 35 per cent; polymorphonuclears, 55 per cent; lymphocytes, 4 per cent and monocytes, 6 per cent. On the first hospital day the patient had a convulsion which lasted several minutes; this was controlled with intravenous sodium amytal.

Treatment included parenteral glucose and saline in amounts ranging from 4 to 6 L. a day. Adrenal cortical extract and penicillin were administered during the first two hospital days. By the third day the patient was improved and the temperature which had developed after entrance had fallen to normal. By the seventh day the non-protein nitrogen had fallen to 50 mg. per cent and the sodium chloride of the blood had risen from 200 mg. per cent to 440 mg. per cent. There was a gradual fall of the alkali reserve from a high upon entrance of 97 volumes per cent to 65 volumes per cent. On the tenth hospital day the urine showed no albumin, no sugar, 2 to 3 red blood cells per high power field and 7 to 12 white blood cells.

There were a few hyaline casts in the urinary sediment. Renal function studies carried out twenty-one days after admission revealed a urea clearance of 33.3 per cent of normal. A repeat examination ten days later revealed a urea clearance of 33.3 per cent of normal. The Volhard test showed concentrations varying from 1.005 to 1.018 on the first examination and 1.008 to 1.016 on the second examination. The Addis count performed on the eleventh hospital day showed 4,900,000 red blood cells, 19,600,000 white blood cells and 46,000 hyaline casts. This was repeated on the eighteenth hospital day and the red blood cells numbered 25,000,000 and the white blood cells numbered 339,000,000. A gastrojejunostomy was performed on the thirty-third day. At operation a large cicatrix at the pyloric area with almost complete obstruction and associated adhesions between the level of the first part of the duodenum and the anterior aspect of the pancreas was found. Two days postoperatively the non-protein nitrogen of the blood had again risen to 103 mg. per cent; the chlorides had fallen to 240 mg. per cent and the alkali reserve had risen to 96 volumes per cent. Change in the blood chemistry developed in spite of adequate pre- and post-operative care. The rise in alkali reserve may have been due to a low reserve type of kidney which was unable to withstand the shock imposed upon it by the surgical procedure. Following surgery, his progress was satisfactory. The blood chemistry returned to normal levels and he was symptomatically much improved. The patient left the hospital against advice ten days after the operation.

Four cases (Cases x to xiii) may be classified fundamentally as diseases of the liver. Three had jaundice and symptoms of the hepatorenal syndrome. In two cases a history of alcoholism was obtained. Prior to entrance one had hematemesis from a ruptured esophageal varix.

The following is a case demonstrating the rôle of severe liver disease in producing extrarenal azotemia:

CASE x. F. H., a sixty-four year old white male, was admitted April 26, 1946. He had been getting progressively weaker for several months and had been unable to work; he had noticed ankle edema for a period of two weeks prior to admission. He admitted some weight loss. There

was no history of clay-colored stools, but his urine had been dark for about one week and visible jaundice had appeared a day prior to entry. The past medical history was non-contributory. He admitted moderate drinking. Physical examination revealed a well developed, well nourished, extremely jaundiced, acutely ill, cooperative but mentally confused white male. The sclerae were icteric and injected; fundoscopic examination revealed normal fundi. The mucous membranes were dry and there was a small hemorrhage in the soft palate. There were no abnormal neck masses or pulsations. The lungs revealed no abnormalities. The heart was not enlarged; there was an occasional ectopic beat and the rate was 80 and the blood pressure was 80/48. The abdomen had several small telangiectatic spots in the skin; it was held tense and there was moderate generalized tenderness. The liver was tender and enlarged to 4 finger breadths below the costal margin. The spleen was not palpable and no other masses were felt. There was a 1 plus pitting edema of the extremities. The genitalia were normal. Rectal examination revealed no abnormal masses. The prostate was normal; neurologic examination revealed physiologic reflexes.

Laboratory examination revealed the following: Urinalysis 1 plus albumin, no sugar, no red blood cells and no white blood cells. Blood: red blood cells, 3,230,000; hemoglobin, 81 per cent; white blood cells, 18,650; bands, 20 per cent; segments, 68 per cent; metamyelocytes, 2 per cent; monocytes, 4 per cent and lymphocytes, 6 per cent. Blood chemistry: non-protein nitrogen, 200 mg. per cent; sugar, 53.3; creatinine, 6.0; NaCl 440. Serology: Wassermann and Kline, negative. Galactose tolerance: normal. X-ray of chest was negative with the exception of an old fractured clavicle on the right side. The heart and lungs were within normal limits. X-ray of the abdomen: The liver appeared enlarged; the kidneys were normal in size, shape and position. ECG was within normal limits.

Treatment consisted of intravenous glucose and saline, a high carbohydrate, high protein and liquid diet, vitamin K and liver extract intramuscularly and amigen intravenously daily. He became progressively worse and delirium increased. Later he developed twitchings of small muscle groups; the pulse became weak

and thready and he expired April 30, 1946, five days after admission.

The following case (Case xv) is one of azotemia in a patient with empyema as a result of pneumonia in the absence of structural renal damage. Dehydration and tissue destruction were prominent as evidenced by the high fever and oliguria. The urine was normal at the time of entrance to the hospital and, subsequently, there was no evidence of renal insufficiency. Albumin, red blood cells and white blood cells were found in the urine during the course of the illness but the urine was normal at discharge.

CASE XV. This patient, a white male laborer sixty-one years of age, was admitted October 2, 1931, complaining of pain in the left chest, chills and fever for several days prior to admission. On physical examination the patient was found to be a well developed, well nourished male, acutely ill. His temperature was 102.8°F., pulse 120 and blood pressure 118/84. Examination of the chest showed consolidation on the left side with typical findings of acute lobar pneumonia. Eight days following admission he became stuporous. Examination revealed an accumulation of fluid in the left chest. Chemical examination of the blood showed a non-protein nitrogen of 94 mg. per cent and creatinine of 3.2 mg. per cent. Urinalysis on admission was essentially negative. Repeated urinalyses at the time the non-protein nitrogen was elevated showed that the patient had a trace of albumin and a few pus cells in his urine. The white blood cell count was 19,500. Hemoglobin and red blood cells were within normal limits. On October 18th the patient had unmistakable signs of empyema involving the left hemothorax. At this time the non-protein nitrogen was 124 mg. per cent and blood creatinine was 4.4 mg. per cent. The urine revealed 2 plus albumin, 8 to 10 pus cells per high power field and 3 to 4 red blood cells per high power field. A few granular casts were found. Three weeks after onset of the illness the left chest was aspirated and fairly thick pus was removed. Two days later a rib resection was done and adequate drainage of the empyema was established. The temperature dropped

to normal, the pulse rate came down to 84 and the non-protein nitrogen which had previously been high returned to normal. The urinary output rose from 500 cc. per day to 1,500 cc. per day. The patient made an uneventful recovery.

A patient (Case xvi) who was studied illustrated extrarenal uremia caused by altered circulation due to coronary occlusion.

CASE XVI. F. P., a fifty-one year old white male, was admitted May 7, 1946, complaining of severe substernal pain, vomiting and mild dyspnea. Illness began two days prior to admission when he was stricken with a substernal pain which travelled from the sternum into the muscles of the arms and shoulders and was accompanied by sweating and vomiting. The patient was a well developed, well nourished male with a temperature of 100.6°F., blood pressure of 98/70 and a pulse of 120. The nail beds and lips were cyanotic; the heart sounds were distinct and of poor quality; no enlargement or murmurs were found. There were moist râles in both bases of the lungs. The liver was enlarged 4 finger breadths below the costal margin and was non-tender. The patient was given pantopon, papaverine and atropine upon admission. Stimulants were administered as well as adrenal cortical extract. The next day orthopnea was less marked but slight pain in the chest persisted and the patient appeared critically ill. His pulse remained rapid and the congestion in his lungs increased. Two days after admission he was dyspneic, slightly confused and restless and complained of pain in the epigastrium. Cyanosis was present, the heart tones were not audible and the pulse was rapid and thready. By the fourth day the patient was more confused, the blood pressure was 70/65, a gallop rhythm was heard, the pulse rate was 110 and the pulmonary congestion increased. He expired on that hospital day.

Laboratory work revealed the following: ECG showed evidence of an anterior wall infarction. Urinalysis: specific gravity, 1.016; microscopic, essentially normal. Blood: white blood cells, 31,400; hemoglobin, 101 per cent; band forms, 20 per cent; polymorphonuclears 63 per cent; monocytes, 2 per cent; lymphocytes, 15 per cent. Non-protein nitrogen, 120 mg. per cent; sedimentation rate, 32 mm.

Two cases of severe dehydration in

psychotic, maniacal and excessively hyperactive patients in whom it was difficult to restore and maintain an adequate fluid balance (Cases xix and xx) were studied. These two had showed oliguria and evidence of dehydration on physical examination. One showed evidence of peripheral vascular collapse and at autopsy evidence of nephrosclerosis was found. It is difficult to state that nephrosclerosis was primarily responsible for the fatal outcome, but this is another excellent example of the rôle of dehydration as the factor in production of azotemia in the presence of a low reserve kidney. The second patient (Case xx) recovered.

CASE XX. A thirty-three year old male negro was admitted March 26, 1946, because of fever. The patient had a known case of catatonic dementia praecox. Physical examination revealed a well developed, restless male. His temperature was 101.2°F.; after several hours it rose to 106.4°F. Respirations were not labored. A marked tachycardia was present, blood pressure was 110/70 and the patient perspired profusely. There was a lenticular opacity of the left eye; the fundus of the right eye was normal. The tongue and mucous membranes were dry. Examination of the chest, lungs and heart revealed no abnormalities. The abdomen was soft and there was tenderness in the left lower quadrant. After twenty-four hours the temperature had dropped to 98°F. and then rose to 102°F. on the third day, followed by a return to normal during the next four days. Three thousand cc. of parenteral fluids were given in the form of glucose and saline on the third day. The patient remained restless and hyperactive. On the sixth day a lumbar puncture was performed which revealed normal dynamics and normal spinal fluid constituents. The blood pressure remained at 110/70; heart and lung x-rays were normal. The patient became less hyperactive and was discharged after twenty-eight days in the hospital. Laboratory work revealed the following: Urinalysis: specific gravity, 1.006 to 1.010; albumin and sugar, negative; red blood cells, 0; white blood cells, 0; casts 0. Blood count: white blood cells 15,200 on entrance and 6,700 on discharge; admission differential, band forms, 12 per cent;

polymorphonuclears, 64 per cent; monocytes, 7 per cent; lymphocytes, 17 per cent. Blood chemistry: entrance non-protein nitrogen, 110.8 mg. per cent (this fell after four days to 85.6 and eleven days later to 30.9); creatinine, 1.4; cholesterol, 213; blood cultures, negative; total protein in spinal fluid, 42 and 1 white blood cell/cc. The patient was discharged clinically improved.

DIAGNOSIS

Although the syndrome of extrarenal uremia is becoming more widely known than before, adequate recognition of this condition is far from satisfactory. The diagnosis is often difficult because the clinical features are bizarre and may be overshadowed by those of the causal primary disorder. To be alert for the presence of this condition is obviously the first essential. The disorder should be sought for in patients who have been vomiting excessively, who have had prolonged diarrhea or in those suffering from severe trauma or infections. Shock, whether due to trauma, surgical operations, burns or heart disease, may precede it. More recently, Barr¹⁸ pointed out the importance of searching for this disorder in postoperative patients who are receiving routine treatment with Wangensteen suction apparatus. One may discover extrarenal uremia in severe liver damage, in Addison's disease, in diabetic coma, or any other kind of coma and in acute severe infection.

If one thinks of the possibility of extrarenal uremia, there are several laboratory measures which establish the diagnosis. The CO₂ combining power of the blood is usually elevated to the point of alkalosis. A study of the blood chlorides reveals hypochloremia in many instances. However, when dehydration resulting from diarrhea is present, the sodium chloride of the blood may be normal and acidosis, not alkalosis, may prevail. The non-protein nitrogen of the blood is always elevated and this constitutes one of the characteristic features of the disorder. Examination of the urine may be helpful in diagnosis. Generally a scanty

urine of low or normal specific gravity is present even when there is dehydration; occasionally the specific gravity is above normal. The urea content of the urine is usually good and the sodium and chlorides are much diminished. With relief of dehydration by adequate fluid administration, the urine volume increases and the specific gravity becomes normal. If, on the other hand, the specific gravity remains fixed, it may be concluded that some permanent renal damage has developed in the course of extrarenal uremia.

The patient may be irrational, irritable, may be in the twilight zone of consciousness or in a deep coma. Convulsions may occur associated with muscular twitchings as observed in genuine renal uremia. All clinical evidences of dehydration are present. The blood pressure is well below normal. There is an oliguria or a complete anuria. The eyeballs are usually sunken and soft and the pulse weak and thready. The patient presents the clinical features common to the state of shock.

TREATMENT

With the diagnosis of extrarenal uremia established, the treatment is directed to restoring to normal the volume and electrolyte composition of the blood. This is accomplished by giving the correct kind of fluid, the proper amount and at the optimal rate of administration.

Three to four thousand cc. a day of a physiologic solution of sodium chloride will usually restore the electrolyte and water balance. If, instead of alkalosis and hypochloremia, acidosis is present, intravenous injections of sodium bicarbonate or sodium lactate are beneficial. In alkalosis, normal saline solution is helpful or ammonium chloride (200 cc. of a 5 per cent solution) may be given intravenously. Hypochloremia is corrected by using physiologic sodium chloride. The underlying condition which is the key factor in bringing on extrarenal uremia must be sought for and corrected.

COMMENTS

There is no unanimity of opinion concerning the exact etiology and pathogenesis of so-called extrarenal uremia although following the earlier papers on extrarenal uremia,⁴⁻¹⁵ many and varied conditions were pointed to as causes. Alkalosis, hypochloremia, a toxic substance from the primary disorder, an excessive elaboration of non-protein nitrogen in the presence of a low reserve kidney, either alone or conjointly, have been held responsible by some.

Conditions common to almost all patients with extrarenal uremia are dehydration, azotemia and oliguria. Low blood chlorides and alkalosis are present in most cases but not in all. Hypochloremia has been said by some to be the cause of azotemia and resultant uremia but this theory has been discarded because hypochloremia is not a constant feature. Others have proposed that alkalosis is the cause but all patients with extrarenal uremia do not have alkalosis as some have acidosis. Vomiting of high intestinal obstruction may develop before alkalosis sets in so that alkalosis cannot be considered a common factor.

Some students (Zondek, Osman and Fishberg) have searched for a common basis in all of the different types of cases. Zondek¹⁹ differentiates extrarenal uremia and extrarenal azotemia. The latter term, he says, designates only those patients with a high non-protein nitrogen in the blood and are not due to renal insufficiency but to an excessive endogenous breakdown of body protein. Good renal function in such cases is shown by the ability to secrete urine with an optimal urea concentration and by satisfactory results of urea clearance tests. On the other hand, in extrarenal uremia there is also extrarenal azotemia but in addition to this there is renal failure. Therefore, in patients with extrarenal azotemia, extrarenal uremia may subsequently develop when renal insufficiency (functional) sets in. Blum and associates⁸ described a condition which they designated as hypochloremic nephrosis. They believed that

the changes were due to the lack of sodium chloride in the system. This, however, is probably another manifestation of extrarenal uremia.

Fishberg²⁰ was the first to suggest the rôle of decreased renal blood flow in extrarenal azotemia. He observed that the primary pathogenic factor in most, if not all instances, is a decrease in blood flow through the kidneys. He points out that in the conditions which lead to extrarenal azotemia, excessive vomiting, hemorrhage, postoperative collapse, diabetic coma, Addison's disease, coronary thrombosis and others are associated with circulatory failure. He believes that the decreased volume of blood flow through the kidneys is of fundamental importance and the basis of nearly all forms of extrarenal azotemia. The shock-like picture represents a deficiency in circulation of the blood and this in turn leads to a deficiency in glomerular activity in extrarenal uremia. After the blood volume is restored to normal the extrarenal uremia corrects itself. At autopsy hardly any changes are found such as are expected in the usual forms of renal uremia.

Osman⁵ believes that the most important factor is the peripheral vascular collapse and this is the chief cause of functional (extrarenal) uremia. The syndrome is explained by Jeghers and Bakst²¹ on the basis of one or more of the following mechanisms: (1) fall of blood pressure; (2) low blood sodium and chlorides; (3) increased protein catabolism; (4) liver damage and (5) renal failure due to low reserve kidney.

Fresh light is shed on the modern conception of renal function by the work of Trueta et al.¹⁷ This work, if confirmed, will have important bearing on our knowledge of renal insufficiency, azotemia and extrarenal uremia. Briefly, these investigators believe that a delicately balanced alternative circulation exists through the renal cortex and medulla, respectively. By appropriate stimulation of the kidney the blood flow destined for the renal cortex is shunted through the vasa recta into the medulla of

the kidney. Following resection of the splanchnic nerves, the blood flow through the cortex is reestablished.

Although the vascular structure of the kidney has been closely studied for many years, complete knowledge is lacking concerning the arrangements and functions of the vasa recta. It is now considered that these structures may be called into play to furnish an alternative route for the blood flowing through the kidney whereby the important cortical circulation may to a variable degree be shut down. This physiologic mechanism may explain what occurs in a variety of conditions such as crush syndrome, renal failure after abortion and lower nephron nephrosis.²² J. Shaw Dunn and Montgomery²³ pointed out in 1941 that in some cases of acute cortical necrosis the blood by-passed the glomeruli and went directly into the medulla by a shorter route than normal. While it is too early to be sure that the mechanism described by Trueta and associates is the common factor sought for in cases of extrarenal uremia produced by a variety of diseases, it is a theory which best explains the disorder.

Previous to this demonstration by Trueta and associates, evidence has been collected which points to a hemogenic mechanism in the production of this type of clinical picture. The term renal anoxia has been coined by Maegraith.²⁴ According to some authors, the prophesy of anoxemia has been fulfilled. They maintain that anoxia resulting from the shunting of blood from the cortex to the medulla explains it. Whether or not this is the mechanism brought into play in trauma and serious illness resulting in extrarenal uremia is not satisfactorily answered as yet but many think favorably of it. It has not been finally determined what stimulations are necessary to bring about this shunting of blood from the greater into the lesser circulation of the kidney. Dehydration which is constantly present has been cited as one possible impulse.

At the present time this work is speculative although interesting and important; further investigations are being made to

determine the rôle of these renal changes in extrarenal uremia.

SUMMARY

1. So-called extrarenal uremia is a functional disease of the kidney which is the result of one or more disorders outside the kidney. There is no unanimity of opinion concerning the exact etiology and pathogenesis of extrarenal uremia although after earlier papers on the subject varied conditions were pointed to as causes. Alkalosis, hypochloremia, a toxic substance from the primary disorder, an excessive elaboration of non-protein nitrogen in the presence of a low reserve kidney, either alone or conjointly, have been held responsible by some writers.

2. Almost any serious illness or injury may be looked upon as a cause for extrarenal uremia and yet there is no common factor accountable for it. Some of the chief clinical characteristics uniformly present are dehydration, stupor, azotemia, low blood pressure and a shock-like appearance. In other cases alkalosis and hypochloremia are present while in others acidosis and normal chloremia exist.

3. Dissatisfaction over the term extrarenal uremia arises because it fails to differentiate the azotemias due to obstructive uropathies from the nitrogen retention of metabolic origin. Interchangeable use of the terms extrarenal uremia and extrarenal azotemia is incorrect for the latter indicates mere retention of nitrogenous substances in the blood depending on factors operating in the absence of functional renal impairment while the former is a symptom complex in which azotemia is always present.

The term is a misnomer when one considers that the chief factors responsible for the uremia occur outside the kidney and yet the ensuing uremia is a result of renal insufficiency.

4. Twenty cases were presented illustrating extrarenal uremia and types of primary diseases which can be held responsible for it, and the suggestion was made that the

common factor may be found in the new experimental work done by Trueta et al.

5. Diagnosis of the syndrome is difficult since clinical features can be overshadowed by the primary disorder. Alertness for the condition is the first essential, especially in patients who vomit excessively, have prolonged diarrhea or who suffer from trauma or infections. Unlike dehydration which causes a craving for water, alkalosis and/or hypochloremia may exist without causing an urge for salt or giving any hint of its presence. The CO_2 combining power of the blood is usually elevated to the point of alkalosis. When dehydration from diarrhea is present, the sodium chloride of the blood may be normal and acidosis may prevail.

6. Treatment is directed toward restoring to normal the volume and electrolyte composition of the blood by intravenous injections of fluids and salt.

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Seminars on Protein Hydrolysates

Chemical Considerations in the Selection of Protein Hydrolysates*

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IT is the purpose of this article to indicate some of the factors which influence the value of protein hydrolysates as adjuncts in the maintenance of optimal nutrition in man. Ultimately it may be possible to describe the requirements of an ideal hydrolysate in chemical terms. However, our present state of knowledge regarding the inter-relationships of chemical constitution and the biologic utilization of proteins and their derivatives is too incomplete to make chemical criteria sufficient for the evaluation of any product. However, there are certain standards that may appropriately be set up and according to these standards there are serious faults in some products. The bases for such criteria may be physical, chemical or biologic since all of these properties are of practical importance.

The value of parenteral hydrolysate therapy has been demonstrated beyond any question. Human subjects have been maintained in nitrogen and caloric balance for many weeks by intravenous feeding alone.^{1,2} The intravenous method in itself imposes stringent requirements not only on the composition of the final product but on the manner of preparation and the control of all steps in manufacture, packaging and use. The intravenous route is chosen only when other methods of feeding are impossible. At present the choice of a product under such circumstances rests on such practical but unsatisfactory factors as freedom from unpleasant or dangerous reaction, the rate of administration that can be

tolerated and ease of storage and handling. It is to the credit of the manufacturers of these preparations that the first of these considerations need seldom be considered. Although progress is being made in the direction of increasing the rate at which nitrogen may be given by vein, the best products still do not permit convenient administration of the large amounts indicated in many postsurgical patients.

The situation with regard to oral protein hydrolysates is somewhat different. Here the final product need not meet the rigid requirements necessary in intravenous preparations as to sterility, non-antigenicity and mineral content. Because of the wide variation in the chemical constitution of protein hydrolysates suitable for oral use, selection of the oral hydrolysate most suitable in a given situation is a difficult matter and one which requires the consideration of many factors.

GENERAL CONSIDERATIONS

Protein hydrolysates consist of a mixture of the hydrolytic cleavage products of protein. Complete hydrolysis results in a mixture of amino acids whereas incomplete hydrolysis produces a mixture of amino acids and peptides. The peptides may be of high molecular weight (proteoses and peptones) or of low molecular weight (a few amino acids linked together). The degree of hydrolysis of a preparation is readily estimated by determining the ratio of amino nitrogen to total nitrogen. Owing to the presence of non-amino nitrogen in some

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amino acids and derivatives, this ratio never reaches 1.0 even with complete hydrolysis but may rise to 0.8. The larger protein fragments may exhibit antigenic properties; hence more complete hydrolysis insures the absence of this undesirable feature and parenteral products usually consist of a mixture of molecules of low molecular weight.

The nutritive value of a hydrolysate depends to a large extent on the parent protein. One of the chief factors determining the biologic availability and usefulness of any protein is the pattern of amino acids of which it consists. From the work of Rose and others³ it is generally recognized that there are about ten amino acids which the human body is unable to synthesize at a rate sufficient to satisfy normal demands. Hence, these amino acids must be taken into the body preformed in amounts sufficient to satisfy the needs of the body. The exact levels at which these "essential" amino acids must be present in the diet are not known. It has been demonstrated that a deficiency of any one of these will lead to poor utilization of the rest and it is probable that the need for each may vary from time to time depending on the particular proteins which need to be synthesized or replaced. An example of the latter point is to be found in the marked differences in the requirements of the growing versus the adult rat.

The remaining twelve amino acids are to be regarded as essential also, but these may be synthesized according to need from nitrogen of a non-specific nature provided there is a source of carbon residues over and above those which must be oxidized.

From these considerations, then, a hydrolysate which is to provide a large part of the nitrogen intake must supply: (1) Adequate amounts of the ten essential amino acids. (2) An adequate supply of total nitrogen in the form of essential or other amino acids. (3) In addition, there must be available material for oxidation, and the vitamins and minerals necessary for proper utilization of the administered nitrogen.

Commercial hydrolysates are derived from a number of protein sources. Since the biologic quality of the product closely reflects that of the protein from which it is derived, selection of starting material must be made with care. Persons on an ordinary mixed diet run little likelihood of developing an amino acid deficiency since the proteins ingested are of widely differing compositions. However, when a single protein or hydrolysate becomes the sole source of nitrogen for even a few days, the problem of its adequacy becomes acute. This is particularly true in view of the fact that hydrolysate usually is given at times when the patient has the greatest need for optimal protein nutrition. Since our knowledge of the requirement of each amino acid is so inexact, we cannot depend upon chemical analysis for evaluation of the adequacy of a preparation. Various biologic tests may be used which have considerable value. Comparison of growth rates of young rats fed the material in question with the rates obtained on a mixed diet or standard protein of known biologic value is one such test. This test suffers from the fault that (1) although the nutritional requirements of the rat resemble in many respects those of man, there may be important differences;⁴ (2) the growth requirements may be very different from those in various kinds of depletion and injury.

Animals depleted of protein stores may be prepared by simple starvation or by more acute technics such as plasmapheresis. The rates of repletion in such animals give valuable information on the relative efficacy of proteins and hydrolysates. Here again may be raised the objection that animal experiments may not provide an adequate basis for the evaluation of expected performance in man. Fortunately, however, animal testing and clinical trial on the same product indicate that animal testing is usually a reliable means of estimating the general performance in man. Ideally, of course, extensive clinical trial on standard cases would be preferable.

Proteins found suitable for complete nitrogen nutrition are usually animal in origin. For large scale production obviously availability and cost are of prime importance and those usually selected are casein, lactalbumin, muscle, blood, liver and yeast protein. Sometimes mixtures of these are used to insure a well balanced product.

Hydrolysis is usually effected by means of acid or by use of proteolytic enzymes. Acid hydrolysis is readily controlled in producing up to essentially 100 per cent hydrolysis. This treatment has the disadvantage of difficulty of removal of the acid by distillation, precipitation or neutralization. Unless very mild conditions are maintained, which prevent maximum hydrolysis, one of the essential amino acids, tryptophane, is completely destroyed and this necessitates fortification of the final product with some other source of this material. Enzymatic hydrolysis is accomplished by incubating the parent protein with a source of proteolytic enzymes such as minced pancreas. The resulting product is an incomplete hydrolysate in which all amino acids remain intact and which contains no added chemicals. Complete hydrolysis is not feasible by such means and the possible presence of large polypeptides must be guarded against. A similar procedure is used with yeast preparations in which the yeast enzymes are allowed to act on the protein. Alkaline hydrolysis is never used since destruction and racemization of amino acids inevitably results.

COMMENTS

Parenteral hydrolysates represent a great contribution to the armamentarium of protein therapy. In cases in which other routes of administration are useless only human blood preparations compete with hydrolysates as sources of nitrogen. Human serum albumin, although stable and effective, is prohibitively expensive. Lyophilized plasma and whole blood are usually reserved for conditions such as shock in which protein deficiency is confined to the circulatory system and prompt repletion is essen-

tial. Here again cost and availability limit the usefulness of these natural materials for use in patients exhibiting extensive depletion and requiring prolonged high protein therapy.

As indicated before parenteral hydrolysates suffer from limitations as to rate and convenience of administration. Several studies have indicated that nitrogen balance can readily be maintained but that positive balance can be attained only with difficulty. However, recently an excellent clinical study by Hoffman and associates,⁵ in which caloric and vitamin content of the diets were controlled, indicates the undoubted efficacy of an intravenously administered casein hydrolysate in attaining markedly positive nitrogen balance in depleted patients with moderately high total nitrogen intake. As much as 13 Gm. of nitrogen per day were retained on a total intake of 26 Gm. per day. Although the authors conclude that the hydrolysate was well utilized, they indicate that an even higher efficiency is obtained upon oral administration. It should be emphasized that such results can be expected only if the other nutritional factors are provided for simultaneously.⁶

In view of the rapid progress being made in the improvement of parenteral preparations there is every indication that safe, concentrated and effective products will soon be available at moderate cost. At the present time selection of a product must be made on the following points aside from the usual consideration in selecting parenteral products: (1) derived from protein of high biologic value with all amino acids conserved in the same pattern as in the protein; (2) non-antigenic (perhaps best guaranteed by high degree of hydrolysis); (3) low concentration of dicarboxylic amino acids (nausea provoking); (4) high rate of infusion; (5) stability (freedom from precipitate on standing).

In selection of an oral hydrolysate other factors must be considered: If the hydrolysate is to be used simply as a minor supplement to an already adequate diet, then the only basis for selection need be

that the biologic value be high and that it be acceptable to the patient. If the product is to form the major part of the nitrogen intake, then care must be taken that in addition to biologic adequacy the preparation must not contain elements which may be harmful in the large quantities likely to be ingested. An example of this is to be found in sodium chloride. Salt is one of the most effective agents in modifying the inherent objectionable taste of hydrolyzed protein. Its presence aids palatability of dilute solutions in amounts as high as 20 per cent. Such a preparation would contain 40 Gm. of sodium chloride if given in a quantity sufficient to provide 24 Gm. of nitrogen. In many postsurgical patients this amount of salt would almost inevitably lead to serious complications of water and salt balance. Care must be taken as with parenteral hydrolysates to include the factors necessary for proper utilization of the nitrogen. Adequate supplementation with vitamins, the minerals necessary for incorporation of nitrogen into protoplasm and adequate calorie coverage by carbohydrate and fat are all necessary.

Since normally ingested nitrogen is chiefly unmodified protein, the question arises as to what justification there is for using oral hydrolysates at all. Most available evidence indicates that any whole protein is at least as well utilized as any modified product from that protein. The advantages to be gained by hydrolyzing proteins may be summarized as follows: (1) They are less bulky and hence have a lower satiety index than natural protein sources. (2) They provide an excellent standard source of nitrogen for the study of many problems relating to protein nutrition. (3) They are usually completely soluble and hence are easy to incorporate into liquid and soft foods. (4) They appear to have some actions not related to their nutritive value which are desirable. As an example Co Tui reports a beneficial effect in obstructed cases. (5) In some cases in which digestion may be impaired they are to be preferred to protein. The first two and to some extent the third of these advantages are shared by a

number of purified whole protein preparations now available.

The disadvantages of oral hydrolysates may be listed as follows: (1) they are accepted poorly by many on the basis of taste; (2) large amounts of concentrated solutions provoke nausea and diarrhea; (3) they are more expensive than natural proteins.

The intelligent selection of a protein hydrolysate is impossible unless the product is labelled clearly with the information outlined in the foregoing discussion. Such labelling should include: (1) Source of protein and method of hydrolysis. (2) Total nitrogen and extent of hydrolysis with method of determination. (3) Vitamin supplement if any. (4) Sodium chloride content. (a) parenteral preparations; essentially salt-free except for special uses; (b) oral preparations; maximum of 4 Gm. sodium for 10 Gm. total nitrogen if used as sole source of nitrogen. (5) Potassium and phosphorus content of oral preparations; both should be present in amounts sufficient to cover the incorporation of one-half the ingested nitrogen into protoplasm. (6) Reference to any deviation from biologic value of the protein or modification of its amino acid pattern.

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Conference on Therapy

Therapeutic Uses of Gamma Globulin

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, *Cornell Conferences on Therapy*, by the Macmillan Company.

DR. RALPH TOMPSETT: Within the past few years there have been important advances in the preparation and clinical use of a number of products obtained by fractionation of human plasma. Some of these have received fairly extensive trial. There is the serum albumin obtained from Fraction v which is used in the treatment of shock, hypoproteinemia and edema. Isohemagglutinins have been isolated from the plasma of group specific bloods and these provide potent materials for blood grouping. Another fraction containing fibrinogen (from Fraction i) has been put to use for the local control of bleeding. From the fibrinogen fraction the material known as fibrin foam has been prepared and is used for local hemostasis in operations on the central nervous system, and also the cellophane-like material known as fibrin film which is employed as a dural substitute. Fraction i has also yielded a globulin material which is presumably deficient in patients with hemophilia. It lowers the clotting time in these patients and is known as the antihemophilic globulin which may be particularly useful in patients with hemophilia who have to undergo surgery.

The product from human plasma which has been used most extensively is gamma globulin, a protein obtained chiefly from Fraction ii which contains the immune bodies against infectious disease. The applications of gamma globulin form the subject of this conference. Dr. Alfred Yankauer will open the discussion.

DR. ALFRED YANKAUER: From the number of cases of measles reported to the Health Department this year (1948) we know we are approaching the peak of a

moderate sized epidemic. Although not as large as the record-breaking epidemic of 1941, it will probably be the largest one since then. Gamma globulin, also called "immune serum globulin (human)," is the most useful prophylactic material available to prevent or to modify measles. This substance is to be differentiated from the one called "human immune globulin" which is the old type of human placental globulin.

Gamma globulin came into widespread use following the American Red Cross Blood Donor Program during the war and the development by E. J. Cohn at Harvard of large scale methods for fractionating plasma. Gamma globulin is obtained from Fractions ii and iii, chiefly from Fraction ii. It can be obtained from outdated blood, even from blood as much as a year old. In fact, preparations separated from frozen plasma four years of age contained antibody titers as high as the material prepared from fresh blood. The antibodies contained in gamma globulin are concentrated about twenty-five times in the process of separation from plasma. Because the pools of adult plasma are obtained from large numbers of donors, the antibody content is quite constant from lot to lot although some interesting variations do occur. After the influenza epidemic in 1943 it was noted that the antibody titer against the influenza A virus rose in the lots of plasma obtained all over the country. It has also been shown that antibodies are present in the blood of easterners against the virus of eastern equine encephalitis but not against the western strain.

At the present time the material in use is not pure enough for intravenous injection and must be given intramuscularly. One

must make sure the material does not get into a blood vessel. It is best given with a large needle, 18 to 20 gauge. The large needle is used because the material is so viscid that it sticks in a smaller gauge needle.

Reactions to gamma globulin are conspicuous by their absence. They occur in less than 1 per cent of cases and usually consist only of mild local tenderness. A few systemic reactions consisting of mild fever for a day or two have been reported but these have been encountered in less than 0.25 per cent of the cases.

Gamma globulin has the interesting property of inhibiting the action of complement *in vitro*. This inhibition can be reversed by the addition of serum albumin to the mixture. It does not occur *in vivo*. In humans very large doses have been used with no effect on complement. This is a property which is of no practical significance at the present time but may prove to be of some significance if a preparation suitable for intravenous injection comes into use.

I would also like to point out that the cost of manufacturing gamma globulin is very high and the administrative difficulties entailed in securing a supply of it are tremendous. Its general use as a prophylactic agent presents problems of quite a different order from that of penicillin or the sulfonamides. It is very expensive and is obtained only from humans.

The principal use for this material in medicine at the present time is to prevent or to modify measles. There have been many extensive and very well controlled studies which indicate that gamma globulin is a valuable and effective agent in preventing or modifying measles. It is well to prevent measles in all very young children and also in some older children or adults under special conditions, such as in states of general debility, pulmonary tuberculosis or other diseases, or in hospitalized patients who might present a hazard to other patients. Prevention of the disease, however, also hinders the development of an immunity against further attacks. For this

reason it is our aim, in older children generally, only to modify measles and not to prevent it. There is the borderline group between the ages of three and five years in which the decision whether or not to modify or prevent measles is a matter of individual judgment. In those over five one should certainly attempt to modify the disease rather than prevent it completely.

In the early studies with placental globulin and convalescent serum it was thought that an important factor determining the effect of the dose was the lapse of time after exposure. It was believed that if the agent was given soon after exposure to measles, it would prevent the disease; if given late, around the seventh or eighth day after exposure, it would modify the disease. Studies with gamma globulin, however, have shown clearly that this is not important in determining whether the disease is prevented or just modified. The deciding factor is the dose. It may be given any time before the eighth day after exposure and it will either prevent or modify the disease, depending upon the dose. A dose of 2 cc. of gamma globulin, the contents of the standard vial now available, will prevent the disease in approximately 95 per cent of exposed, susceptible household contacts under the age of one, approximately 80 per cent in the ages of one and two, 70 per cent in the ages of three and four and 60 per cent in the ages of five and six. I should emphasize that these results are not from exposures at school or other casual exposures of one sort or another. They are obtained from individuals who are susceptible to measles and who have been intimately exposed at home.

The dose of gamma globulin used for the prevention of measles is 0.2 cc. per Kg. and the dose required for the modification of measles is 0.04 to 0.05 cc. per Kg. It is convenient to remember the dosage in terms of the standard 2 cc. vial. In general, a dose of 2 cc. prevents the disease in the age group in which measles should be prevented and modifies the disease in the older group in which measles should be modified.

I would like to point out that modified measles is a disease essentially different from regular measles. The incubation period may be lengthened, the disease is milder and many of the ordinary signs of measles may be absent. The duration of immunity from gamma globulin is no longer than two or three weeks and may be less. It is very difficult to know the exact duration of immunity because multiple exposures are so common. When loss of passive immunity is indicated in a given child by the development of measles, it is often impossible to tell which exposure was the cause of the disease.

Thus far, I have discussed the use of gamma globulin as a prophylactic following exposure to measles. Before we proceed to the consideration of other uses, it should be mentioned that in the *treatment* of measles gamma globulin is of no practical importance.

Acute infectious hepatitis is another disease in which gamma globulin has proved useful. Extensive studies in the Army and a number of studies in institutions have been reported. These leave little doubt that gamma globulin is effective in preventing acute infectious hepatitis. In control groups eight to twelve times as many individuals developed acute infectious hepatitis as compared to those exposed in whom gamma globulin was used. The doses have ranged from 0.12 to 0.3 cc. per Kg. In one study in adults a standard dose of 10 cc. proved quite effective. Again, this agent has no value in the *treatment* of this disease once it has developed.

The use of gamma globulin in the prevention of acute infectious hepatitis should be differentiated from its use in attempts to prevent homologous serum hepatitis. We have no evidence that gamma globulin itself spreads homologous serum hepatitis. It has been used in an attempt to prevent this disease in some extensive Army studies involving about 6,000 individuals who had been given blood transfusions. Doses of 10 cc. had no effect in preventing the disease. It did seem to lengthen the incubation period. After larger doses, namely,

20 cc. given in two fractions, there was some indication that it might prevent the disease; but in the particular study in which this observation appeared, there were not enough cases to make it statistically significant. However, this matter is probably of no practical importance because it is not feasible to give gamma globulin to everyone who receives a transfusion.

The available preparations of gamma globulin are of no value in the prophylaxis of mumps. Moreover, even large doses of gamma globulin are of no value in the treatment or prevention of mumps orchitis. However, gamma globulin prepared from the plasma of patients convalescing from mumps has apparently been partially effective in preventing mumps orchitis. The 20 cc. dose of gamma globulin from patients convalescing from mumps, incidentally, was equivalent to about 4,000 cc. of normal adult plasma.

Gamma globulin has been shown experimentally to act in scarlet fever in the same manner as scarlet fever antitoxin or convalescent serum. Large doses have to be used. At present it is not of practical importance in the prophylaxis or treatment of this disease.

In pertussis gamma globulin from normal individuals is of no apparent value, but the gamma globulin from hyperimmune pertussis serum is useful in the treatment and prevention of whooping cough when it is used in the same way as hyperimmune serum. The material is prepared by fractionation of the plasma from previously hyperimmunized donors. It is on the market at the present time although it is still expensive.

In experimental animals human gamma globulin has some effect in the transmission of the disease but it has never been tested prophylactically in man. It is probably impossible to do so since it would have to be used in very large numbers of people and the doses would have to be repeated throughout the summer months to make sure of the effect. In one well controlled study its use

in the preparalytic stage of poliomyelitis was found to be without value.

German measles has achieved notoriety in recent days because of its apparent effect on the fetus of the pregnant woman. We have no published reports on the use of gamma globulin in German measles. We are familiar, however, with its use in a few small institutional outbreaks. From the results in these we are doubtful of its value in the prevention of German measles. The same applies to chicken pox. Here also we are familiar with a few outbreaks in which gamma globulin did not seem to be very effective in the dosage used. It has been tried in epidemic diarrhea of the newborn, both prophylactically and therapeutically, with no effect. A trial has also been made in an influenza outbreak in a children's institution. No effect in preventing or modifying the disease was noted with the dosage used. It was tried therapeutically in an outbreak of upper respiratory infection of unknown cause in a large institution but without effect. Finally, I should mention that the material has been given to premature babies without noticeable effect on the regaining of birth weight, on mortality or on any of the other factors that were measured.

In summary, gamma globulin has two important uses: first, as an agent for preventing or modifying measles; and second, for the prevention of acute infectious hepatitis in institutional outbreaks. The New York City Health Department gives the material to physicians who desire it for their patients under five years of age who are household contacts of cases of measles. The Health Department also provides it for patients above the age of five if the physician thinks there is some special reason for protecting the particular individual. In addition, it may be obtained for use in institutional outbreaks of measles and certain other special situations.

DR. TOMPSETT: There must be many questions you want to ask Dr. Yankauer. The mechanism of action of gamma globulin is of a good deal of interest. What is

known about the antibody content of this material? Despite the effectiveness of gamma globulin in the cases Dr. Yankauer has mentioned, there still seems to be a little bit of black magic about why it works. The amount of antibody added to the patient's normal supply by the usual dose of gamma globulin seems to be so small. Can anyone tell us about the antibody titers? The particular disease in which gamma globulin is most helpful is the one in which it is especially difficult to measure antibodies. How much do we know about that, Dr. Yankauer?

DR. YANKAUER: There is no way of measuring the titer of measles antibodies.

DR. TOMPSETT: In connection with gamma globulin what antibodies are measured?

DR. YANKAUER: The titer of mumps antibodies has been used a great deal. There are others, including scarlet fever antitoxin, diphtheria antitoxin, streptolysin and fibrinolysin. I think the antibodies against influenza and poliomyelitis have also been measured. I can cite more specific data on mumps antibodies. The titratable antibodies against mumps virus are ten times as high in convalescent serum as in normal serum, and twenty-five times as high in gamma globulin as in adult pooled serum. Whether this measures the factor responsible for the therapeutic result when gamma globulin is injected is another question, and I do not think we know the answer. There may well be other important factors in gamma globulin which cannot be measured in the laboratory.

DR. TOMPSETT: That is also my thought. Even a large dose of gamma globulin, namely, 10 cc., which would represent the antibody content of 500 cc. of whole blood would only increase the normal person's blood antibody content by about 10 per cent on the basis of the data you cited in connection with mumps. This would amount to ten times as much or doubling of the normal person's blood antibody content if the 10 cc. of gamma globulin had been obtained from convalescent serum. We do not know what antibody titers are necessary

for protection but since such increases in antibody content are not particularly striking it appears to me that some factors other than the added supply of antibodies might play a part in therapeutic results.

DR. YANKAUER: I would agree with that.

DR. TOMPSETT: Are there other questions?

DR. WALSH McDERMOTT: I would like to ask Dr. Yankauer about the gamma globulin obtained from the serum of persons convalescing from mumps. First, is it available in commerce and, second, is it of any value for the prevention of orchitis when given after the parotitis has become evident?

DR. YANKAUER: The material is not available in commerce. It was manufactured just for a specific study. It prevents orchitis if it is given within the first twenty-four hours after the parotitis has developed.

DR. McDERMOTT: How much mumps convalescent serum would have to be administered to obtain the same effect?

DR. YANKAUER: The dose of gamma globulin from serum of convalescent patients was 20 cc.; and since the antibody of the serum is concentrated approximately twenty-five times in gamma globulin, the dose of the serum would be 500 cc.

In mumps as in measles the use of large doses of convalescent serum has yielded equivocal results. Some studies reported favorable results in preventing mumps orchitis and some in preventing measles. I think the answer to the problem lies in the matter of dosage. Another aspect of this may be cited.

There has been one study of measles reported in which very large doses of gamma globulin given early in the course of the measles, but before the rash, seemed to have some effect in modifying the disease. It is very difficult to evaluate this result, of course, and only the one study has been made. The possibility of such use of gamma globulin was known from the observation that large doses of convalescent serum given early after measles had developed apparently modified the course of the disease.

DR. TOMPSETT: Are there any other questions?

VISITOR: It was mentioned that modified measles is a different disease. Is the danger of post-measles encephalitis decreased in measles modified by gamma globulin?

DR. YANKAUER: I believe that no such complication has yet been reported in a case of modified measles. I do not know of any cases of encephalitis after measles that had been modified. I would like to hear about it if anyone knows of such an occurrence.

SAME VISITOR: Do you believe that gamma globulin if given early after the development of symptoms of measles would prevent encephalitis?

DR. YANKAUER: I do not think there is enough experience with the material to be able to answer that. Encephalitis is quite a rare complication although a very serious one.

DR. TOMPSETT: There is every reason for believing that non-modified measles confers immunity against that disease. However, when the disease is altered as it is in modified measles, the question arises whether the immunity is not also changed. I wonder if Dr. Stimson can throw any light on that.

DR. PHILIP STIMSON: Regarding the immunity resulting from modified measles, I think the consensus is that, if there is enough measles to give a rash, the patient will develop a protective immunity. If the modification of the measles is carried so far as to eliminate the rash, the patient does not secure full immunity.

There are two other points which I would like to bring up. One relates to the indications for modifying measles. The Board of Health states in effect: "We will supply the gamma globulin for children up to 5 years old, and for such patients over 5 as the doctor thinks need it." It is my opinion that every susceptible person, without exception, who is known to be exposed to measles should be given at least a modifying dose of some form of protective medication. The second point relates to the preparations. Among the various concerns who

supply so-called gamma globulin, there are some who mix it with placental extract. Do you know how we can distinguish these products from those which contain only gamma globulin?

DR. YANKAUER: I am sorry I cannot answer that.

DR. TOMPSETT: Dr. Stimson, you brought up one point which, while it may be of no great importance to the practicing pediatrician, is very important to those in the home with a case of measles. In statements regarding the use of gamma globulin for the prevention or modification of measles, authors use the term "exposure." They never define it. What do you consider to be an "exposure"?

DR. STIMSON: One must consider as an "exposure" any reasonably close contact, such as in the home or at school, with a child who within four days after the contact develops the rash of measles. Count back three days from the appearance of the rash in the exposing child and you have the first day in which it was possible for the patient to transmit measles.

DR. TOMPSETT: Why is gamma globulin so effective in measles and not in scarlet fever?

DR. STIMSON: There is an interesting theoretic explanation. Gamma globulin is derived from pooled blood of the general population. Ninety per cent of the adults over twenty years of age have had measles but only 10 or 12 per cent have had scarlet fever. One might, therefore, expect the antibodies to be in much higher concentration against measles than against scarlet fever. Very large doses of gamma globulin may reduce the incidence of complications in scarlet fever somewhat, but the result is not very striking. I think that the value of the serum does not lie solely in the antibody titer. For example, 10,000 units of scarlet fever antitoxin and 100 cc. of human convalescent serum are comparable in regard to clearing up the rash and neutralizing the toxic manifestations of scarlet fever, but the 100 cc. of convalescent serum has far fewer units of antitoxin.

DR. TOMPSETT: What is your opinion of the duration of action of gamma globulin, Dr. Stimson?

DR. STIMSON: I would expect it to be protective a little longer than two weeks, perhaps up to three weeks, since it is in effect a homologous serum. The protection obtained from the heterologous horse serum cannot be counted on for as long as two weeks. I have seen diphtheria develop as early as eight days after a prophylactic dose of diphtheria antitoxin although that is quite unusual.

DR. TOMPSETT: Are there other questions?

STUDENT: What did Dr. Yankauer mean when he distinguished home contacts from school contacts in regard to the dosage schedules of gamma globulin?

DR. YANKAUER: In the studies carried out for the evaluation of gamma globulin in measles only household contacts were used. That is an important point because school or institutional contacts have a much lower attack rate. It has been shown that a susceptible individual intimately exposed to measles in the home is much more apt to contract it than one exposed only in school. Also, the spread of measles is more likely to occur in the crowded home with poor hygiene. The National Health Survey showed clearly that measles occurred at an earlier age and spread more extensively through the family in the substandard areas. It was in these families that this dosage schedule was evaluated, but I did not mean to imply that the doses mentioned were for use only on this kind of contact.

SAME STUDENT: Is it the usual practice to give gamma globulin to school contacts?

DR. YANKAUER: As I mentioned before, it is the policy of the New York City Department of Health to supply gamma globulin only for household contacts under five years of age and for institutional contacts. That would include nursery school contacts but not children in grade school. This policy is to some extent influenced by the supply. The material is difficult to obtain. The present supply was secured from the Red Cross during the war. It is quite adequate

at the present time and with current policies, but eventually it will have to be replenished. The future supply of this material will depend on the national blood bank program of the American Red Cross. The policy is based on the important fact that measles has a high mortality rate in children under five years of age. Eighty-five per cent of the deaths occur in that age group. Its use is being restricted to the most important group although the plan to modify measles in all individuals may be a sound one.

DR. STIMSON: Preparations of gamma globulin can be bought in the drug store nowadays at \$2.75 or \$3.00 per vial. The price has recently gone down.

DR. TOMPSETT: I telephoned a drug store today at 3 P.M. and the current retail price quoted to me was approximately \$2.25 per cc.

Dr. Yankauer, you mentioned the possibility of protecting an individual against the development of infectious hepatitis. Would you give gamma globulin to other members of the family if one individual in the family developed hepatitis? My understanding of the present status of infectious hepatitis is that it is really not very infectious under ordinary living conditions although it is quite infectious in Army camps and the like. Families want to know whether they should be given gamma globulin when one member develops infectious hepatitis.

DR. YANKAUER: It is difficult to be certain of the wisest practice in such cases. As Dr. Tompsett stated, there have not been many instances resulting from the familial spread of the disease. It is certainly possible for such spread to occur.

DR. TOMPSETT: We can state, can we not, that the danger of spread within a family is not great?

DR. YANKAUER: It does not appear to be.

DR. McDERMOTT: I would like to ask another question about measles. It was mentioned that among the patients who have received preventive or modifying doses of gamma globulin, some have febrile

illness presumed to be measles but without a rash. I would like to know how frequently such illnesses are observed. I realize the difficulty in making the diagnosis of modified measles. What interests me is the possibility that adults may develop measles many times but with a rash only once. Is there evidence that measles can be so modified as to occur without a rash?

DR. YANKAUER: Yes, I would say that there is such evidence. Cases of mild illness, with fever, conjunctivitis and perhaps a slight cough but no rash occur with sufficient frequency at the proper time after exposure when gamma globulin has been given, that it seems justified to assume they represent modified measles. It seems unlikely that they are due to some other virus infection. I wonder what Dr. Stimson would say to that.

DR. STIMSON: I think it is not an unusual experience to aim for modification and produce so much modification that one is left uncertain as to whether the slight fever is due to measles or to something else.

DR. TOMPSETT: Are there any other comments?

DR. STIMSON: There is one point I would like to stress about the actual administration of gamma globulin. One has to inject it within a very short time after loading the syringe because of its tendency to stick in the syringe.

DR. TOMPSETT: There is a long period of time, let us say during eight days after exposure to measles, when one can use gamma globulin effectively. Is it the same dose whether given on the first or last day of the period?

DR. YANKAUER: In actual practice the available period does not extend from the first to the eighth day. One usually does not know that a child has been exposed to measles until the exposing child develops a rash. Ordinarily, by that time four days have passed. From the studies with gamma globulin I would say that the dose would be the same whether given at the beginning or the end of the period in which it is known to be effective.

SUMMARY

DR. GOLD: In one of our conferences on therapy held in 1941 the topic of discussion was the use of human convalescent serum against infectious diseases. The object was to confer passive immunity for prophylaxis or for treatment in infectious diseases by the administration of antibodies obtained from humans. Human convalescent serum proved to be effective in prophylaxis against measles, in the prevention and cure of scarlet fever and there was some indication that it might be of value in mumps and whooping cough. There were serious obstacles in the way of the general development of this kind of therapy. The doses were large, the cost was high and human convalescent serum was available in only limited amounts and through special sources, as in the case of the Manhattan Convalescent Serum Laboratory which was affiliated with the Department of Health of New York City.

This conference on the uses of gamma globulin is, in a sense, an extension of that subject in line with the developments which have taken place in the past few years. Dr. Edwin J. Cohn and his collaborators at Harvard Medical School devised a method for the large scale fractionation of plasma. It has been found that the protein fraction, termed "gamma globulin" in the form in which it was isolated, contains the major portion of the antibodies against infectious diseases. The solution of antibodies obtained from human plasma or serum has now become an article of commerce and is readily available at fairly reasonable cost. It is provided by several manufacturers in 2 cc. vials under the name of "immune serum globulin (human)." It represents an approximately 16 per cent solution of gamma globulin containing the antibodies present in normal pooled plasma but in a concentration about twenty-five times that of the original plasma. In the short period of time since the isolation of this material, its utility has been explored in a number of diseases: measles, scarlet fever, mumps, whooping cough, German measles, chicken

pox, infantile diarrhea, poliomyelitis, serum hepatitis, infectious hepatitis and influenza. Thus far it has proved most effective in the prophylaxis of measles and infectious hepatitis. There is some indication that it may prevent homologous serum hepatitis and that large doses may act in a manner similar to convalescent serum in the prophylaxis or treatment of scarlet fever.

The subject is still in the experimental stage. Evidence now exists indicating that some specific diseases in which gamma globulin prepared from normal pooled serum is not effective may respond to gamma globulin obtained from the plasma of patients convalescing from the disease. Thus, while the so-called "immune serum globulin (human)" has not been found effective in mumps, large doses of gamma globulin prepared from the plasma of convalescent patients have proved effective in preventing mumps orchitis, and gamma globulin prepared from the plasma of hyperimmunized donors has been found useful in the treatment and prevention of whooping cough.

The use of gamma globulin in measles was discussed in some detail. The material now available is apparently without value after the disease is established and its use is restricted to prophylaxis. When the material is given at any time between the first and eighth day after exposure, it will either prevent measles or reduce measles to a very mild disease (modified measles) depending upon the size of the dose. The view was expressed that modification of measles is desirable in most cases since this apparently allows the patient to develop full immunity while passing through a very mild form of the disease, and that the prevention of the disease is desirable in only special cases as in very young infants and under other conditions in which an active measles would give rise to special hazards either to the individual or to contacts.

The discussion also covered some of the details of administration and raised questions concerning the mode of action of gamma globulin. The current material is

suitable only for intramuscular injection and is toxic by intravenous injection. The dose for complete prevention of measles is 0.2 cc. per Kg. and only about one-fourth of that, namely, 0.05 cc. per Kg. for the modification of measles. Local and systemic reactions occur in about 1 per cent of the cases and are usually mild. An interesting point concerning the mechanism of action

was raised, namely, whether the results obtained with gamma globulin are due solely to the addition of antibodies to the patient's blood. There is some indication that the amount of antibodies so added may be too small to account for the protective effects and that some factor other than added antibodies may be, at least in part, responsible for the therapeutic results.

Clinico-pathologic Conference

Acute, Severe Chest Pain with Fatal Termination*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, G. M., (B. H. History No. 62249), was a forty-six year old white, married, packing house worker who entered the Barnes Hospital for the first time in 1937 following an automobile accident in which he suffered abrasions of the scalp and right shoulder and a fracture of the left knee. At that time his blood pressure was 145/90 and there was suggestive expiratory wheezing over both lung fields but physical examination, except for the traumatic injuries noted, was otherwise negative. The laboratory data, likewise, were all within normal limits. His hospital course was entirely uneventful.

He sought admission for the second time on May 30, 1947, complaining of pain in the chest. The family history was irrelevant. He stated that in his childhood he had "bronchitis" and at the age of thirty had undergone repair of a right inguinal hernia. His general health had apparently been excellent and he was able to perform rather strenuous work in the packing house in which he was employed. He denied any history of previous chest pain. The systemic review was unrevealing. Of interest, however, was the fact that the patient had drunk and smoked excessively for many years.

There was some indication that for approximately one year the patient had noted slight shortness of breath on infrequent occasions when excited, and he had noted transient swelling of the ankles for about the same period. In general he had felt quite well until the night before entry

when he complained of a feeling of "severe tightness" over the left chest which did not radiate. He took very little food at suppers but shortly thereafter vomited some yellowish material. The sensation of pressure in the chest persisted all night and shortly after its onset the patient stated that he became short of breath. The next morning the chest pain gradually became worse and a short while before the patient presented himself in the emergency room of the Barnes Hospital the pain became crushing in character; he found it most difficult to breathe and began to perspire profusely.

At the time of entry the temperature was 36.4°C., pulse 100, respirations 34 and blood pressure 90/70. The patient was an obese white male who appeared acutely and critically ill. Although he had been given morphine immediately on entry, his pain persisted and he answered questions with difficulty. The respirations were rapid and shallow. The skin was flushed and the patient perspired profusely. Slight cyanosis of the lips and fingernails was noted. Examination of the eyegrounds was negative. The upper respiratory tract was entirely normal. The trachea was in the midline. Examination of the lungs revealed resonance to percussion, but coarse ronchi and moist bubbling râles were heard throughout the right lung field and over the left lung to a lesser extent. The heart was somewhat enlarged, the left border dullness extending 10 cm. to the left of the

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

mid-sternal line in the fifth interspace. There was no right-sided enlargement. The rhythm was regular except for an occasional premature ventricular contraction. The sounds were described as being "fair to poor" in quality and at the apex a gallop rhythm was heard intermittently. There were no murmurs. The right radial pulse was somewhat faint; the left was of better quality. The peripheral vessels were moderately sclerotic. Normal pulsations were felt in the arteries of the lower extremities. The abdomen was obese and slightly distended but no tenderness or masses were elicited. The herniorrhaphy scar was well healed. There was 2+ pitting edema over both lower extremities. The fingers were not clubbed. Neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 5,100,000; hemoglobin, 13.5 Gm.; white cells, 18,000; differential count: stab forms, 7 per cent; segmented forms, 80 per cent; lymphocytes, 9 per cent; monocytes, 4 per cent. Urinalysis: albumin, 3+; sugar, negative; sediment, 20 to 30 white cells per high power field with occasional red cells. The stool examination was guaiac negative. Blood Kahn test: negative. Blood chemistry: sugar, 163 mg. per cent; non-protein nitrogen, 27 mg. per cent; total protein, 5.6 Gm. per cent; albumin, 3.7 Gm. per cent; globulin, 1.9 Gm. per cent. Corrected sedimentation rate (Rourke-Ernstene): 0.3 mm. per minute. Electrocardiogram: high peaks in the T waves in leads I and II; no other abnormalities were seen.

As noted the patient had been given 15 mg. of morphine on his admission to the emergency room from which he was sent immediately to the ward and placed in a cardiac bed. Oxygen was administered by a positive pressure mask and rotating tourniquets were applied. The patient was given 0.25 Gm. of aminophylline intravenously. The blood pressure rose gradually to 100/80 during the first hour and several hours later it was recorded as 120/90. After a second injection of morphine the patient

rested quietly although he continued to perspire profusely; his skin remained cool. At 9 P.M., approximately ten hours after entry, the patient coughed up about 1 ounce of material containing two large blood clots, one apparently old and one fresh. At that time examination of the chest revealed diminished breath sounds and ronchi over the left lower lung field. For the next few hours the patient continued to cough up bright red blood in small quantities. There was no calf tenderness and Homans' sign was negative bilaterally. The calf measurements were equal. The patient spent a fairly comfortable night and the next morning complained of no pain but shortness of breath was still apparent, the respirations being 30 per minute. Examination of the lungs revealed ronchi bilaterally and slightly diminished breath sounds at the left base. The heart sounds were of fair quality. The pulse was thready at a rate of 90 and the blood pressure had again fallen to 90/60. Two + pitting pretibial edema was still present. Reexamination of the optic fundi again showed no significant changes.

Another electrocardiogram was obtained. There was a diminution in the height of the T waves in leads I and II. Multiple precordial leads showed no changes in the S-T segment. During the course of the morning ronchi persisted throughout both lung fields. The heart sounds continued to be of moderately good quality and the rhythm remained regular. No gallop rhythm was audible. The skin had become warmer and the profuse perspiration had ceased. The patient's temperature was 37°C., and his pulse had risen to 105. The abdomen was slightly distended but no other significant findings were noted on physical examination. A repeat white blood cell count was 22,000 and the corrected sedimentation rate was 0.4 mm. per minute. The patient's condition continued as described without change until 9:30 P.M. in the evening of the second day when he suddenly developed pulmonary edema and, despite all emergency measures, died shortly thereafter.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Before we discuss this case in detail I should like to ask Dr. Massie if he would make a comment on the electrocardiograms described in the protocol.

DR. EDWARD MASSIE: Although two electrocardiograms were described in the protocol, actually three were taken. The first, which was obtained at the time of admission, was in general a perfectly normal tracing. The heart rate was slightly increased to 102 to 104 per minute. The second tracing, taken a few hours later, showed no significant change from the first. The T waves were perhaps slightly lower than those seen in the first tracing but I would not be able to attach significance to either of these two records. The third set of tracings, taken during the morning of the patient's second day—the day on which death occurred—showed perfectly normal findings in leads I, II and III. Likewise, the six chest leads revealed no significant deviations from the normal.

DR. ALEXANDER: The problem presented in this case is indeed a common one—the identity of a lesion which gave rise to chest pain. Actually we have few specific clues as far as the clinical findings are concerned. I do not believe that the physical findings on cardiac examination give us much assistance but certainly one of the diagnoses which would come to mind immediately would be coronary occlusion. Dr. Massie, would you care to comment on this possibility?

DR. MASSIE: The history as it is recorded is certainly typical of coronary thrombosis. This patient developed chest pain which came on not suddenly but rather gradually. As the pain continued the patient became progressively ill, his blood pressure fell and he developed pulmonary edema. The one atypical feature in this instance is that the patient coughed up blood. Hemoptysis is not prominent in coronary thrombosis but of course can occur with certain complications. Considering the case as a whole, myocardial infarction is certainly a very good possibility.

DR. ALEXANDER: You did not take into consideration the absence of electrocardiographic findings. In a patient who had myocardial infarction would you not have expected changes to be evident at this stage of the process? The first tracing was obtained about thirteen hours after onset of the patient's pain and the final one probably forty or forty-five hours afterward.

DR. MASSIE: I agree that usually one would expect to see some suggestive changes within twenty-four to forty-eight hours of the infarction whereas, as we have just noted, tracings obtained in this case were normal. The absence of electrocardiographic changes constitutes strong evidence against myocardial infarction, particularly in view of the fact that the episode was severe enough to cause the patient's death on the second day.

DR. ALEXANDER: In other words, if no electrocardiograms had been taken, you would be more willing to accept the diagnosis of myocardial infarction than you are in view of the normal tracings?

DR. MASSIE: Yes, I think that sums up the situation quite well.

DR. CARL V. MOORE: I would like to ask Dr. Massie if he thinks the lack of electrocardiographic changes may have been due to the fact that the infarct was in the interventricular septum? Is it not true that without esophageal leads one cannot always rule out an infarct at that particular site?

DR. MASSIE: I think your point is well taken but I would be very much surprised if one would find no evidence of an infarct in any of the chest leads. In practically all instances even small lesions in the interventricular septum will lead to some changes in the chest leads. Recently, at the meetings of the American Federation for Clinical Research in Chicago, a paper was presented in which it was pointed out that although esophageal leads may furnish additional evidence of interventricular septal infarcts that procedure nonetheless is not essential. If this patient had had a septal infarct, I should have expected to find some conduc-

tion defect or some abnormality in the apical chest lead.

DR. ALEXANDER: For about a year before entry this patient apparently had had some shortness of breath and a history of transient ankle edema. Taking these findings and adding to them râles in the chest and albuminuria, could one make a fairly good case for some form of heart disease?

DR. MASSIE: I do not believe that this patient had significant chronic myocardial or valvular lesions.

DR. W. BARRY WOOD, JR.: I should like to ask Dr. Massie how he explains the fact that this patient developed acute left heart failure if he had had neither myocardial nor valvular disease. What other explanation is there for the signs of cardiac insufficiency which this man exhibited?

DR. MASSIE: I do not believe that he necessarily had heart failure. He had a history of chronic bronchitis in the years past, and I should think that the dyspnea and ronchi could have been due to chronic pulmonary disease. I am thinking, for example, of emphysema, chronic bronchitis or even bronchial asthma. I agree that terminally there was acute heart failure as indicated by pulmonary edema, but I believe pulmonary edema resulted from an acute lesion which must have affected either the myocardium or the associated greater vessels.

DR. WOOD: You will recall that the patient had ankle edema for over a year.

DR. MASSIE: That is true but on the other hand he took rather large quantities of alcohol and perhaps had either a nutritional deficiency or hepatic dysfunction.

DR. WOOD: I was impressed, Dr. Alexander, by the diastolic blood pressure of 90 which was recorded at the time that the patient was in the hospital in 1937 after his automobile accident. It seems entirely conceivable to me that the symptoms which occurred during the year prior to his final admission may have been due to hypertensive cardiovascular disease.

DR. ALEXANDER: Dr. Schroeder, do you have any comments to make on that point?

DR. HENRY A. SCHROEDER: I think Dr. Wood's suggestion is well taken. If this patient really had a persistent diastolic pressure of 90 in 1937, it is most likely that it would have risen in the ensuing ten years. It is true, of course, that some patients maintain a diastolic pressure of 90 to 100 mm. of mercury for many years without developing serious hypertension. But ten years previously, when this patient was only thirty-seven, if his diastolic pressure had been 90, it is quite likely that it would have subsequently become higher.

DR. ALEXANDER: Do you believe this man had coronary artery disease?

DR. SCHROEDER: I do not think that he had a significant amount of coronary arteriosclerosis.

DR. ALEXANDER: What other diagnoses should be entertained?

DR. JOSEPH C. EDWARDS: The presence in the urine of albumin and white cells seemed to me to be significant and I think that the diagnosis of pyelonephritis merits consideration.

DR. ALEXANDER: Since pyelonephritis is accompanied by hypertension in about 50 per cent of cases, it may have constituted the underlying lesion which subsequently led to hypertensive cardiovascular disease. I should like to ask Dr. Sale if he believes that this man could have had a dissecting aneurysm.

DR. LLEWELLYN SALE, SR.: I think that that diagnosis certainly has to be entertained although the history is not entirely typical. It would be helpful if we had a more accurate knowledge of the patient's blood pressure in the year prior to entry.

DR. ALEXANDER: It is true that a history of hypertension is of some value in making a diagnosis of dissecting aneurysm but certainly we have seen the lesion in patients who have had no hypertension. I think that the diagnosis of dissecting aneurysm is favored by the description of the chest pain which was said to have been "crushing;" that is rather typical. One of the reasons that a better history of the patient's blood pressure prior to this episode would be

helpful is that in dissecting aneurysms the fall in blood pressure at the time of the acute episode is usually not as great in magnitude as is the case in myocardial infarction.

DR. SALE: On the other hand, the patient was apparently in shock and marked hypotension is, of course, a usual feature of shock.

DR. ALEXANDER: That is true but I have actually seen patients with dissecting aneurysms who had all the classical signs of shock except that their systolic blood pressure, even to the terminal stage, remained at levels of 140 mm. of mercury. Dr. Smith, do you have any comment? Which of these two diagnoses would you care to support?

DR. JOHN R. SMITH: I think diagnoses of myocardial infarction and dissecting aneurysm have to be entertained in parallel. I actually favor the former for it seems to me that the general features and the clinical course of this man's illness was more typical of myocardial infarction than of dissecting aneurysm. The lack of electrocardiographic change does not disturb me although such changes certainly are seen in the majority of cases. Electrocardiographic changes may, however, be delayed for days, particularly if an infarct occurs in a region of the myocardium which has been previously damaged.

DR. ALEXANDER: Either of the two lesions may give rise to intense pain. Would you comment on the pain, Dr. Smith?

DR. SMITH: There are two schools of thought on the mechanism of pain in myocardial infarction. One group believes that the pain comes from fibers in the adventitia of the coronary vessels themselves and that distention of the vessels proximal to an area of thrombosis initiates the pain. The other theory holds that ischemia of the heart muscle irritates the visceral afferent fibers from the heart. These fibers course in the cardiac nerve from the myocardium through the cardiac plexus. They travel through the sympathetic chains without synapsing to the dorsal spinal nerves. Some pass through the stellate ganglion while most others pass through the upper five dorsal roots. It is

thought that in a few patients fibers pass through the cervical sympathetic chain and it is this route which is thought to account for the pain in the face which occasionally accompanies angina pectoris. In others there is a generous supply of visceral afferent nerves running to the right side, and in those people anginal pain may radiate to the right arm and right chest. Afferent fibers from the aorta, in general, have the same pathways as those from the heart.

DR. SCHROEDER: I should like to differ with Dr. Smith and support the diagnosis of dissecting aneurysm of the aorta, probably in the ascending arch. I agree with Dr. Smith, however, that the absence of electrocardiographic changes does not rule out myocardial infarction since as he stated they may certainly appear quite late in the course of that lesion.

DR. ALEXANDER: I recall from the protocol that the right pulse was somewhat fainter than the left radial pulse. Unfortunately, differential blood pressures on the two sides were apparently not taken. Does this finding substantiate the diagnosis of dissecting aneurysm, Dr. Schroeder?

DR. SCHROEDER: It might if actual measurements had shown a difference in pressure in the two arms although in perfectly normal patients the blood pressure readings may be different in the two arms. Unless one knows for certain what the situation was prior to the acute episode he cannot draw definitive conclusions. It should be stated, however, that if the difference is marked then the findings usually take on real significance.

DR. ALEXANDER: Dissecting aneurysms usually occur in the ascending aorta. If a dissecting aneurysm is to explain diminution in the right radial pulse, one must assume that the dissection involves the innominate artery since the right subclavian artery comes off of the innominate. Usually if the innominate artery is involved, the internal carotid is likewise affected, and in this patient there were no clinical findings to suggest such an occurrence.

DR. WOOD: Dr. Alexander, may we ask Dr. Robert Moore to comment on the pathologic lesion in dissecting aneurysms?

DR. ROBERT A. MOORE: Dissecting aneurysm of the aorta is most frequently associated with either simple chromatropic degeneration of the media or with idiopathic cystic medial necrosis. Actually the latter is merely an advanced stage of the former. As Dr. Alexander pointed out dissecting aneurysm usually occurs in the ascending aorta; actually almost all dissections are limited to the first 5 cm. of the aorta. It is thought that the combination of medial necrosis plus the systolic thrust of the heart are the two factors which lead to actual rupture. The line of rupture almost invariably is transverse which is the reason for the postulation that lengthening of the aorta during the systolic thrust is the immediate provoking factor. It is of interest incidentally that the rupture always occurs two-thirds of the distance from the lumen of the vessel and one-third of the distance from the outside. There is one further point which I should like to make. It is often thought that an arteriosclerotic plaque in the intima gives rise to or is responsible for dissection of the aorta. Actually there may or may not be an intimal arteriosclerotic plaque at the site, but it is thought that it is not significant in the causation of dissection.

DR. PALMER H. FUTCHER: In regard to the inequality of the radial pulses we have just consulted the patient's chart and there is a definite note by Dr. James G. Hirsch, who saw this patient, that the blood pressure at the time of his examination was equal in both arms, being 115/90. Dr. Hirsch made a further note, however, substantiating the fact that on palpation the right radial pulse did seem weaker than the left.

DR. MASSIE: I think one other diagnosis should be considered, namely, that of pulmonary infarction.

DR. ALEXANDER: That is a good suggestion. This patient had edema of his lower extremities. He had râles in the chest, chest pain and hemoptyses. Although there was no calf tenderness, Homans' sign or other

local evidence of phlebothrombosis, we must consider pulmonary infarct. Dr. Goldman; do you have any comment in regard to Dr. Massie's suggestion?

DR. ALFRED GOLDMAN: I agree that pulmonary infarction should be considered; I do not believe it can be completely ruled out. I should like to point out, however, that hemoptyses may complicate dissecting aneurysm for there may be dissection along one of the bronchial vessels or the aneurysm may actually rupture into the lung.

DR. WOOD: I should like to ask Dr. Virgil Scott to comment on hemoptyses in connection with aortic aneurysms. Does the occurrence of hemoptysis mean that the aneurysm has necessarily ruptured into the bronchus, or may bleeding occur without rupture?

DR. VIRGIL C. SCOTT: No, bleeding may arise as a result of pressure of an aneurysm on the bronchus or pulmonary tissue and does not necessarily indicate rupture, at least in syphilitic aneurysm.

DR. ALEXANDER: Is not the situation rather different in syphilitic aneurysms than it is with dissecting aneurysms, in that in syphilis the aneurysm tends to be saccular?

DR. WOOD: That is a good point, Dr. Alexander, but this patient had hemoptysis for almost twenty-four hours before he died and had the dissecting aneurysm ruptured into his lung he certainly would not have lived that long.

DR. EDWARD H. REINHARD: I saw a patient recently who would be of interest to discuss in this regard. The patient had coughed up blood repeatedly for several weeks. It was thought that he probably had carcinoma of the bronchus and upon bronchoscopy blood was seen coming from the left lower lobe bronchus. The x-ray findings did not aid us in establishing a diagnosis. The patient was subjected to exploratory thoracotomy and, much to our surprise, was found to have a large aneurysm of the descending thoracic aorta. The wall of the aneurysm was intact and the patient is still alive. We assumed that the bleeding had been due to erosion of the

aneurysm into the left lower lobe. May not a similar situation have obtained here?

DR. LEO J. WADE: One other cause of hemoptysis may be mentioned. In the presence of chronic passive congestion of the lung patients may cough up blood. Certainly we see that occur in mitral stenosis for example. This patient had râles in his lungs and conceivably may have had hemoptysis as a result of pulmonary hypertension.

DR. STANLEY HAMPTON: I favor pulmonary infarction rather than dissecting aneurysm for I have been impressed by the fact that in the latter pain in the back rather than in the chest is characteristic.

DR. ALEXANDER: Dr. Smith, may one differentiate between pulmonary infarction and dissecting aneurysm or myocardial infarction on the basis of the intensity of the pain? Which would be apt to be most severe?

DR. SMITH: Either lesion may cause excruciating pain. Probably dissecting aneurysm more consistently causes greatest pain and agony.

DR. ALEXANDER: In summary, it seems that the chief possibilities in this case are dissecting aneurysm and myocardial infarction although pulmonary infarction has received some support. I believe that the consensus of opinion favors dissecting aneurysm because it would best fit all the findings, but I think we shall have to await the pathologists' findings in order to learn the identity of the lesion.

Clinical Diagnoses: ? Dissecting aneurysm of the aorta with possible erosion into a bronchus of the lung itself, ? myocardial infarction, ? pulmonary infarction.

PATHOLOGIC DISCUSSION

DR. FRANK VELLIOS: When the sternum was removed at autopsy there were 200 cc. of bloody fluid in the right pleural cavity. The left pleural cavity was obliterated by fibrous adhesions and over the lower lobe of the left lung there was a calcified focus 7 cm. in diameter and 1 cm. in thickness. In the posterior mediastinal tissue there was

a massive hemorrhage which extended laterally under the calcified plaque behind the lower portion of the left lung.

The pericardial sac contained 5 cc. of clear fluid. The heart weighed 490 Gm. and the ventricular walls were markedly thickened; that of the left ventricle measured 28 mm. In the interventricular septum there were a few small foci of firm white fibrous tissue. There was a slight degree of arteriosclerosis of the pulmonary arteries and a few small yellow plaques were present in the descending portion of the aorta. Just distal to the ostium of the left subclavian artery there was a small transverse rent in the intima of the aorta which opened into a space within the aortic wall. This space extended distally for 20 cm. and divided about half the anterior circumference of the wall of the thoracic aorta into two layers, the inner of which was approximately twice the thickness of the outer. The dissected cavity within the aortic wall communicated superiorly and proximally in the region of the rent in the intima with the tissues of the mediastinum. All these tissues and spaces were infiltrated with fluid and clotted blood.

The liver weighed 1,970 Gm. and was markedly congested as was the spleen. The kidneys weighed 180 Gm. each. The cortical surfaces were slightly granular and there was one depressed scar in the left kidney.

DR. R. A. MOORE: Although the primary lesion in this case was a dissecting aneurysm of the aorta which ruptured into the mediastinum and extended particularly into the peritruncal tissues of the left lung, there were a number of features unusual to the lesion. Knowing the nature of the anatomic findings in this case, I was in a rather embarrassing position when I was asked, during the clinical discussion, to comment on the probable site of dissecting aneurysms for I knew I would mislead the clinicians. This aneurysm originated 1 cm. beyond the ostium of the left subclavian artery; taken with some of the other anatomic findings this observation casts light on the symptomatology of the case. A

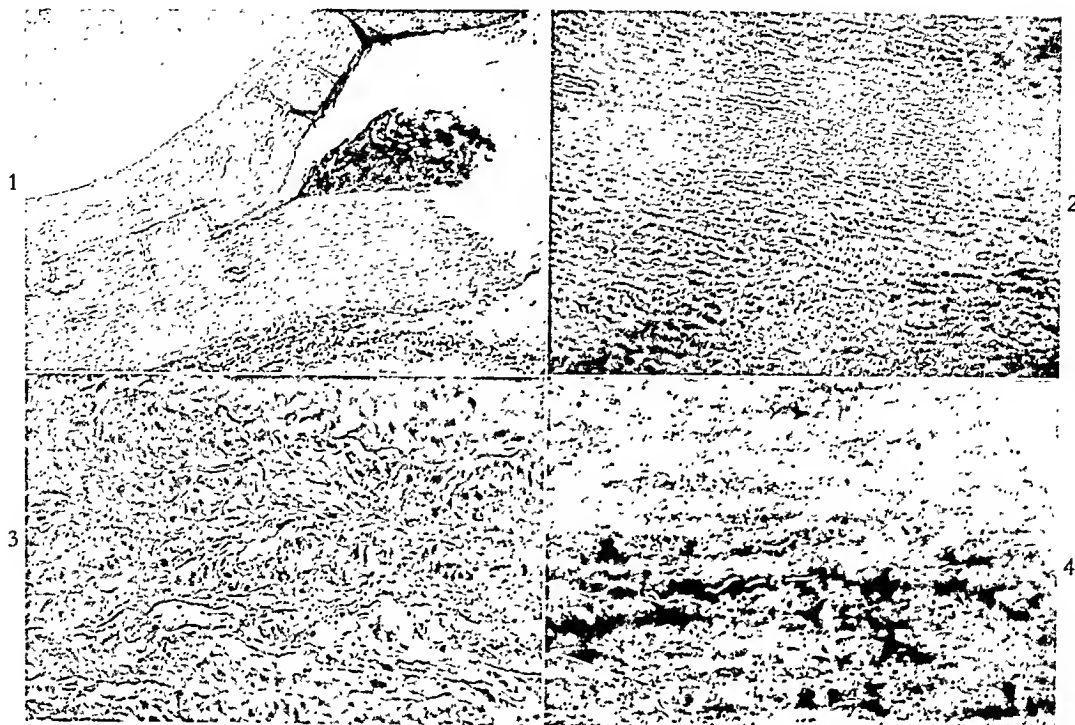


FIG. 1. Wall of the aorta at the advancing edge of the dissecting aneurysm with separation of the media by a hemorrhagic mass.

FIG. 2. Wall of the aorta with broad longitudinal band of necrotic fibers and chromatropic degeneration of adjacent viable fibers.

FIG. 3. Higher magnification of focus of chromatropic degeneration of the aortic media with small cystic foci between the elastic fibers which resemble the lesion of idiopathic cystic medial necrosis.

FIG. 4. Section stained to demonstrate fat in which the fatty degeneration which is part of chromatropic degeneration takes a dark stain.

second unusual finding was that the dissection was directed only distally and did not extend proximally toward the heart; thus, there was no *anatomic* basis for the development of the signs and symptoms of occlusion of one of the coronary arteries as occurs not infrequently in patients who have a more typical lesion. A third factor of interest was that since this dissection involved about 50 per cent of the anterior circumference of the aorta, it did not affect the intercostal vessels which arise posteriorly. The dissection also did not involve the innominate, carotid or subclavian vessels and therefore no signs or symptoms related to interruption of the circulation of any of these appeared; there was no anatomic explanation for the clinical observation that the left pulse differed in intensity from the right.

Still another feature which marks this case as an unusual one lies in the fact that in

most instances the aneurysm would have ruptured into the pleural cavity and there would have been rapid exsanguination and death. As the entire left pleural cavity, however, was obliterated by fibrous adhesions the blood dissected into the mediastinum and through the pleura so that blood accumulated there and about the peritracheal tissues of the lungs. Dissection proceeded in the peribronchial tissues in much the same way as is seen when an aneurysm ruptures into the hilum of the lung. We did not demonstrate the anatomic defect where blood entered the bronchial system, but in my experience lesions such as this often rupture into one of the smaller bronchi.

In summary then, Dr. Alexander, this case of rupture of the aorta is unusual in comparison with most dissecting aneurysms. I believe the clinicians are to be commended on their attempt to make the correct

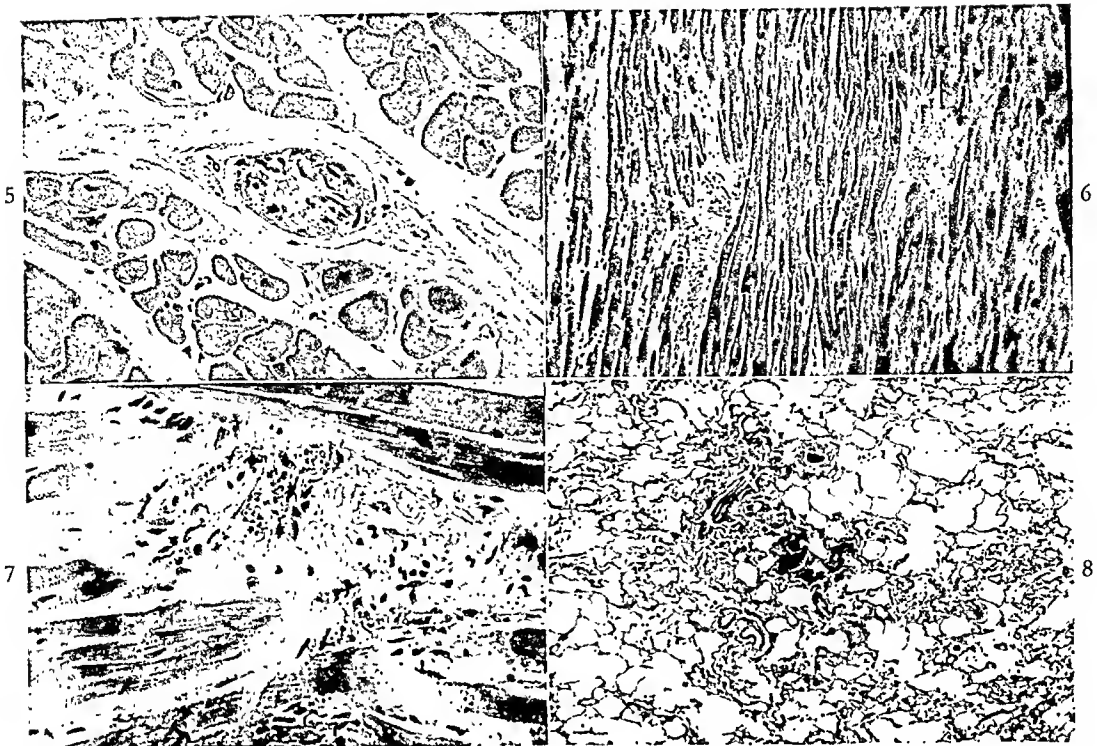


FIG. 5. Thickened arteriole in the myocardium with accompanying slight increase of interstitial fibrous tissue.

FIG. 6. Myocardium showing fragmentation and segmentation of myocardial fibers, slight increase of interstitial fibrous tissue and a focus of activated Anitschkow myocytes.

FIG. 7. Higher magnification of a focus of activated fibrous tissue with Anitschkow myocytes in the myocardium.

FIG. 8. Focus of hemorrhage and "heart failure" cells about the peribronchial tissues in the lung.

diagnosis in view of the fact that the clinical picture was altered because of the anatomic position of the rupture, the presence of pleural adhesions and other factors mentioned which forced this disease to take a somewhat different course than it usually takes.

The first photomicrograph (Fig. 1) has been selected from the border of the advancing margin of dissection near the diaphragm. One can see the aortic wall being torn apart by the fluid and clotted blood between the separated layers. The lumen of the aorta is above and the adventitia below. The dissection at this point was atypical in that it lay approximately midway between the lumen and the adventitia; in other parts of the lesion, as was pointed out in the gross examination, the findings were more typical, the inner portion being approximately twice as thick as the outer layer.

Figure 2 is a section from the aortic wall

just above the point of rupture in the region of the ostium of the left subclavian artery. There is a horizontal strip of tissue through the middle of the section which has undergone complete necrosis while the tissue on each side is viable although not normal. Such a longitudinal area of necrosis in the aorta is fairly common in this disease, but I do not think that enough emphasis has been given in the literature to the relation of this change to the cause of the dissection.

Figure 3 is a higher power view of the previous section and shows the typical lesion of chromatropic degeneration; in one or two areas a lesion suggestive of idiopathic cystic medial necrosis is seen as evidenced by several definite foci in which there is no tissue. These foci contain pale basophilic, metachromatic material which stains with thionin. This substance has accumulated between the elastic fibers and in association with it there is necrosis of the immediately adjacent tissue.

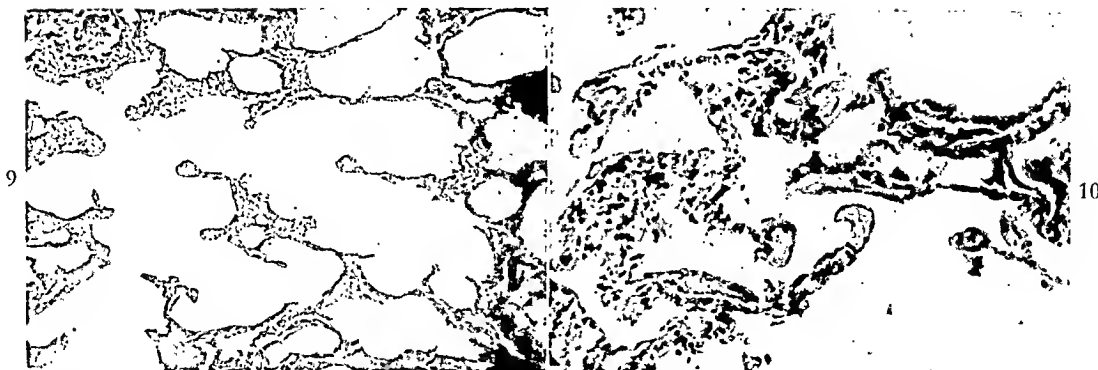


FIG. 9. Clubbing of the ends of ruptured alveolar walls in the lungs.

FIG. 10. Alveolar capillaries of the lung filled with dense, acidophilic, homogeneous precipitate of proteinaceous nature.

The next section (Fig. 4) is also from the aortic wall; the light lines represent the elastic tissue and the black masses are specifically stained for fat. This change is also one of the pathologic evidences of chromatropic degeneration—fatty degeneration of the tissues of the aortic media with accumulation of fat on the surface of the individual elastic fibers.

Now let us consider the relation of this lesion to hypertension. Dissecting aneurysm of the aorta definitely occurs more frequently in patients who have hypertension. The pathologist certainly cannot make a diagnosis of hypertension *per se*, but in this patient, whose heart weighed 490 Gm., there was no other evident cause of hypertrophy and dilatation. When that observation is considered along with the finding of microscopic changes in sections of the kidney, which include thickening of the arterioles, thickening of the parietal layer of Bowman's capsule, thickening of the basement membrane of the glomeruli and slight diffuse increase in connective tissue throughout the kidney—in other words, slight arteriolar nephrosclerosis—the probability that this patient had hypertension is above 90 per cent, and possibly above 95 per cent.

In Figure 5 an arteriole in the heart is seen which shows definite thickening. There was widespread thickening of the arterioles throughout the body, indicating that the patient had generalized arteriolar sclerosis. The myocardium exhibited the effect of

coronary insufficiency as evidenced by scattered small foci of increased fibrous tissue and loss of myocardial fibers. The insufficiency, however, was not of the usual sort due to arteriosclerosis of the larger vessels; rather it was apparently the result of arteriolar sclerosis; there was actually only slight arteriosclerosis of the major coronary arteries.

Figure 6 is from the heart and illustrates two interesting changes: First, there is a focus in the left central portion of the section which represents an activation of fibrous tissue in the heart muscle; this change is indicated by the proliferation of Anitschkow myocytes and is seen under a variety of conditions. Second, fragmentation and segmentation of the myocardial fibers is present. There has been a good deal of discussion as to the significance of this latter change. Dr. Otto Saphir of Chicago maintains that fragmentation and segmentation of the myocardium indicates that two conditions were in existence shortly before death: one, coronary insufficiency of such a degree as to bring about some state of slight degeneration of the myocardium and second, a sudden dilatation of the heart within the last forty-eight hours of life.

Figure 7 is a higher magnification showing proliferation of the Anitschkow myocytes in the perivascular connective tissue with development of a nodule. Many of the so-called Aschoff bodies which have been produced experimentally in animals are nothing but small nodules of proliferation

such as these; they are to be distinguished from the true Aschoff bodies seen in rheumatic fever by the absence of fibrinoid change. No fibrinoid change is present here and this type of reaction, therefore, is non-specific.

In Figure 8 a section of the lung is seen; there is a mass of "heart failure" cells and red blood cells at one point immediately adjacent to some peribronchial tissue. Such a lesion is frequently confusing. It may cast a radiographic shadow which looks very much like miliary tuberculosis. This finding constitutes evidence that, at least in some instances, the blood which finds its way into the alveoli when failure of the heart develops may be present because of actual rupture of given capillaries or small vessels rather than as a result of generalized diapedesis of red cells. In the former instance, therefore, a mass of blood may be seen in some areas and not in others. The heart failure cells are filled with hemosiderin.

This patient did have a certain degree of emphysema, and in Figure 9 there is a beautiful demonstration of what has been described in the literature for many years as the "club-ended alveolar walls" in which local fibrosis supposedly results following rupture.

The last section (Fig. 10) is of another incidental lesion for which I had hoped we might find some explanation in the discussion of this case history. In many of the pulmonary capillaries the entire lumen was occluded by granular and homogeneous acidophilic precipitate with the appearance of plasma. I thought that this man might have had some plasma concentration although the total blood protein was only 5.6 Gm. per cent at the time a determination was made during his illness. Certainly at the time of his death when the fixative acted on whatever was inside the pulmonary capillaries it precipitated a material that had a high concentration of protein.

Pathologic Diagnoses: Chromotropic degeneration of the media of the aorta; dissecting aneurysm of the descending thoracic aorta; rupture of dissecting aneurysm into the mediastinum with hemorrhage into the mediastinal and retropleural tissues, along the peritruncal tissues of the lungs and into the lower lobe of the left lung; serosanguinous hydrothorax, right (200 cc.); arteriosclerosis of the abdominal aorta, moderate; of the thoracic aorta, pulmonary and coronary arteries, slight; arteriolar sclerosis, generalized, slight; arteriolar nephrosclerosis, slight; hypertrophy and dilatation of the heart (490 Gm).

Visceral Neuropathy Complicating Diabetes Mellitus*

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ALTHOUGH the coexistence of neurologic findings and diabetes mellitus has been recognized for perhaps eighty years, diabetic neuropathy has become a clinical entity only recently. This has been due in large measure to diligent observation on the part of several able clinicians working in busy diabetic clinics.^{1,2,9,12} Their reports have stimulated others to an increasing awareness of the condition. There are, of course, a few who question the validity of diabetic neuropathy. The question is raised as to the specific relationship of this syndrome to diabetes. Although no definite proof has been brought forth to establish such a specific relationship, this syndrome is certainly seen most commonly in diabetics.

For the sake of brevity we have used the designation, "diabetic neuropathy," throughout this report to indicate a symptom-complex occurring most frequently, but not necessarily exclusively, in diabetic patients without intending to imply anything concerning its etiology. An excellent and by far the most comprehensive review of the subject by Rundles in 1945 has served to crystallize our knowledge of diabetic neuropathy in general and of its visceral manifestations in particular.¹ He has clarified the clinical picture of neurologic signs and symptoms and has stressed the involvement of the genito-urinary and gastrointestinal systems. Although the frequency of this complication is not great in his series of 3,000 diabetics (about 4 per cent), the high degree of correlation becomes apparent when one considers the background of

neglected or poorly controlled diabetes and marked weight loss.

The following case is of interest because it so strikingly represents what has now come to be recognized as classical diabetic neuropathy with involvement of the somatic and autonomic nervous systems superimposed upon a background of inadequately controlled diabetes and great weight loss. The good immediate therapeutic result in this case illustrates the fact that thorough investigation and vigorous treatment are not in vain.

CASE REPORT

M. P., a thirty-three year old, white male truck driver, presented himself on September 12, 1947, complaining of a "cold" of two weeks' duration. He had had rhinorrhea during this period and a cough productive of thick yellow sputum of three days' duration. Anorexia had been present for several weeks and there had been nausea during the previous two weeks.

The patient had been a known diabetic since 1937. There had been four episodes of diabetic coma. For the past two years he had noted protuberance of the lower abdomen but without marked distress. He had had difficulty in emptying his bladder and there was a history of nocturnal incontinence. There was very little urgency. He had had diarrhea occasionally without fecal incontinence. During the two weeks prior to entry there was severe constipation. He frequently had episodes of vertigo when changing from a recumbent to an erect position. He complained of numbness of the legs, especially in cold weather, as well as aching legs and burning of the feet much of the time. There had been fleeting needlelike sensations in the arms, legs and trunk; there had been no

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disturbance of gait. He had been impotent for some months. Dimness of vision had been present for an indefinite period. There was no history of luetic or of gonorrheal infection.

The patient had been taking 37 units of protamine zinc insulin for three months but had been partaking of an inadequate diet, frequently omitting entire meals. His weight was 30 pounds below the normal figure for his age and height.

Physical examination revealed an emaciated and extremely apathetic man. There was marked pallor and weakness. The blood pressure was 108/80, respirations were 18 and the pulse was 96. The pupils were small and reaction to light was almost imperceptible. Funduscopic examination revealed many shiny plaques, exudates and punctate hemorrhages of the retina. The cranial nerves were otherwise intact. The lower abdomen was protuberant. The urinary bladder was palpated at the level of the umbilicus. The prostate was not enlarged. Rectal sphincter tone was normal and the rectum itself was filled with hard feces. All tendon reflexes were absent. There was no disturbance of sensation or of proprioception including vibratory sense. Skeletal muscle development and tone were poor.

Catheterization yielded 1,300 cc. of residual urine. The urine contained innumerable pus cells; *Aerobacter aerogenes* and a non-hemolytic streptococcus were grown on culture. A lumbar puncture revealed normal spinal fluid dynamics. The Pandy, Ross-Jones, Wassermann and Lange tests were negative. There was no increase in cells. An intravenous urogram taken shortly after entry demonstrated dilatation of both renal pelves and ureters. (Fig. 1.) Roentgenographic examination of the gastrointestinal tract revealed delayed gastric emptying. The head of the meal was in the proximal colon at four hours and in the transverse colon at six hours while barium remained in the stomach. (Figs. 2A and B.) There was evidence of disordered motor function of the small intestine with scattering, segmentation and hypertonicity as well as diminution of the mucosal folds.

Significant laboratory data included: fasting blood sugar, 380 mg. per cent during the early part of the hospital stay; blood urea nitrogen, 15 mg. per cent; blood Wassermann and Kahn tests, negative; the admission blood count revealed the following: hemoglobin, 13.3 Gm.; erythrocyte count, 5,230,000; leukocyte count, 15,900; hematocrit, 43 per cent; differential



FIG. 1. Intravenous urogram showing dilatation of the ureters and kidney pelves.

count, 75 per cent neutrophiles; corrected sedimentation rate (Wintrobe), 36 mm./hour. There was no ketonuria at any time.

A urethral retention catheter was inserted at the time of admission. The urine became grossly bloody several hours afterward, although the catheter had passed easily without apparent trauma. Cystoscopic examination revealed marked hyperemia, edema and bullae formation. There was a small band of fibrous tissue in the region of the posterior urethra, not sufficiently large to produce significant obstruction.

On the fifteenth hospital day 1.9 Gm. of gray, fibrous, non-vascular tissue was resected trans-urethrally. There was no glandular tissue in the specimen which was reported as showing chronic urethritis. The retention catheter was removed on the third postoperative day. Prostigmine (1:2,000) was administered hypodermically every three hours from the fourth to the eighth postoperative day. When prostigmine was stopped, bladder distention without dysuria recurred. Although the bladder was distended to the level of the umbilicus, the patient stated that he had no desire to urinate. Resumption of prostigmine promptly improved bladder evacuation.

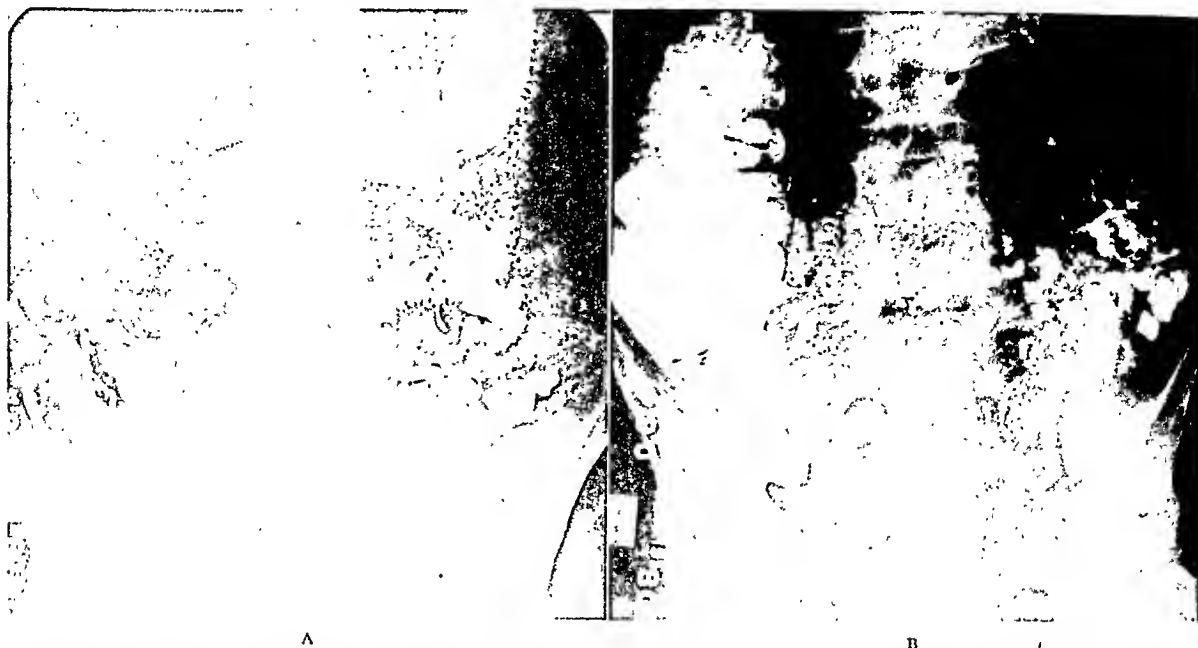


FIG. 2. A and B. roentgenograms taken four and six hours after a barium meal. Note the delayed gastric evacuation and the disordered motor function of the small intestine.

In addition to the therapeutic measures already enumerated the patient received 4 Gm. of streptomycin daily over a nine-day period pre- and postoperatively. Alkalinization of the urine was achieved with the administration of 8 to 12 Gm. of sodium bicarbonate daily. Postoperatively he received sulfonamides and intramuscular penicillin for ten days. He was given a diet consisting of 350 Gm. of carbohydrate, 120 Gm. of protein and 100 Gm. of fat. Supplemental vitamins (A, B, C and D) in moderate doses were given orally. He received a maximal dose of 60 units of protamine zinc insulin and 40 units of crystalline insulin per day.

About ten days before his discharge from the hospital the patient began to display increased strength and improved appetite. Anorexia and nausea had subsided; he was taking all of the prescribed diet. At the time of discharge the insulin requirement was 26 units less than the previous maximum total daily dose. He was instructed to continue the diet as outlined. Meeholyl bromide (oral), 200 mg. three times a day, was substituted for prostigmine when he left the hospital. He was emptying his bladder well at this time. He was discharged on the twenty-seventh hospital day.

Development of bilateral phlebothrombosis of the calf muscles of the legs necessitated readmission to the hospital four days later. The response to anticoagulation therapy was good.

There were no embolic phenomena. A fasting blood sugar prior to discharge was 179 mg. per cent. The patient had gained 7 pounds since his first hospital admission forty days previously.

On November 12, 1947, the patient reported that he felt very well. There was no weakness and there were no digestive symptoms. Although the urinary stream was not forceful, there was no incontinence or abdominal swelling. Dizzy spells were less severe and less frequent. He was having satisfactory sexual intercourse for the first time in a year. Aching of the legs and burning of the feet were no longer present. He still complained of dimness of vision. He had gained 11 pounds. Physical examination revealed all the neurologic findings previously described. The blood pressure in recumbency was 164/110 in the right arm and 150/108 in the left arm. The pulse rate was 100. In the erect position the pressure fell to 64/? over a five-minute period. The pulse rate rose to 120 and was barely perceptible. There was no syncope or giddiness. There was no distention of the urinary bladder. The retinal findings as described were still present. There was profuse pyuria. It was believed that the diabetes was satisfactorily controlled.

On March 13, 1948, six months after beginning treatment, the diabetes was still well controlled. Except for occasional dizzy spells, he felt quite well and was working regularly.

There had been no urinary symptoms and only an occasional white blood cell was found in the urinary sediment. His vision was somewhat improved and fewer hemorrhages were visible in the retina. His weight was 18 pounds greater than at the initial examination.

COMMENT

This case exemplifies the development of neurologic complications in a patient whose diabetes had been grossly neglected. The disease was serious enough to have resulted in diabetic coma on four occasions. Several workers, notably Jordan, have attempted to show that the occurrence of this complication bears no relation to the severity of the disease while others have stressed the importance of weight loss and uncontrolled diabetes in the majority of cases.¹⁻³ In Rundles' series of 125 cases with neuropathy 75 per cent had lost over 25 pounds in weight. It is of interest to note that our patient belonged to the younger age group. Jordan believes that neuropathy affects old rather than young patients; however, 25 per cent of the patients in Rundles' series were under forty years of age. Our patient was thirty-three years old when first seen, but he had had urinary retention for two years.

While there is evidence of some vesical neck obstruction in the case presented, we believed that it is the result of a neuromuscular defect leading to urine-stasis and severe cystitis of long-standing. The minor degree of obstruction, the lack of a sense of urgency in the presence of an enormously distended bladder and the favorable response to parasympathomimetic drugs would seem to confirm this opinion. The supervening mechanical defect which may be less amenable to treatment as it progresses suggests the necessity for early recognition and treatment of the neurogenic disorder.

Rudy and Muellner, in their review of eleven cases of neurogenic bladder complicating diabetes, thought that the prognosis was fair in properly treated patients. Jordan presented twelve cases of genito-

urinary dysfunction, seven of these with urinary retention. In the latter series urinary retention persisted indefinitely. Rundles found eighteen cases of neurogenic bladder in 125 cases of diabetic neuropathy. He noted the almost invariable association of impotence as occurred in our patient.

The relationship between diabetic retinopathy and neuropathy is undetermined. However, several studies, especially that of Folk and Soskin, suggest the close correlation between the development of retinopathy and poor diabetic control.⁸

This patient also showed evidence of orthostatic hypotension. This phenomenon was observed in eight patients of Rundles' series.

The occurrence of disordered motor function of the gastrointestinal tract in diabetic neuropathy has been recognized less frequently. Rudy has reported a case of mucosal atrophy and disordered motor function of the stomach in a diabetic with neurologic signs and symptoms and a poor nutritional background.⁴ Rundles reported four cases of gastric retention and disturbed small bowel motility in his series of 125 patients with neuropathy although 61.8 per cent of the entire group had gastrointestinal symptoms, consisting of constipation, diarrhea, anorexia or nausea. However, it is well known that diabetics like other groups may have an organic disease or functional disturbances of the gastrointestinal tract unrelated to the primary disorder.

The so-called deficiency pattern is seen in a variety of diseases. It is primary, for example, in idiopathic steatorrhea but it may occur as a secondary manifestation in other disorders, such as ulcerative colitis, tuberculosis, Addison's disease and carcinoma. The roentgenographic signs include: (1) hypermotility and hypertonicity; (2) hypomotility and hypotonicity, later; (3) segmentation; (4) scattering effect; (5) delayed gastric evacuation. Pathologic examination may reveal mucosal atrophy; exaggeration of the mucosal folds may result from disturbed physiology of the

muscularis mucosa. This disordered motor function is non-specific and almost always occurs in association with malnutrition.⁵ Inglefinger and Moss demonstrated the inability of the intramural plexus to liberate acetylcholine in sprue.⁶ May, McCreary and Blackfan showed that injection of mecholyl improved intestinal movement and glucose absorption in celiac disease.⁷ The flat oral dextrose tolerance curve in nutritional disorders may be explained by: (1) slow gastric emptying and (2) disturbed motility and mucosal changes in the small intestine. That disordered motor function of the small bowel may be part of a vicious circle in the malnourished diabetic can be readily appreciated. It is conceivable that poor control and malnutrition leading to the bowel changes just described may serve to further the state of malnutrition and impede recovery.

The mechanism of diabetic neuropathy remains obscure. Rudy has been the proponent of vitamin B deficiency.⁹ There seems to be little evidence for this point of view. Most of the patients show no other evidence of vitamin deficiency; the diets of patients with neuropathy usually contain adequate thiamine; polyneuritis resulting from thiamine deficiency is a late finding.^{1,2,10,11} Several workers have found thiamine ineffective in the management of this complication.^{1,2} Other clinicians believe that arteriosclerosis is an important factor.^{2,10,12} In spite of our ignorance of the etiology of this complication most workers agree that poor management, neglect and consequent malnutrition are important factors.

The good response to therapy in this case indicates that treatment of this complication is not hopeless. Diabetes must be well controlled. We should like to stress the importance of a diet adequate in calories and in protein content for only with such a diet can positive nitrogen balance be restored and clinical recovery be expected. Good diabetic control with only a basal diet is inadequate. The urinary tract must be investigated for a possible obstructive lesion. Slight vesical neck obstruction as the

result of long-standing bladder paralysis and infection may prevent a favorable outcome; such a defect if found should be treated surgically. The use of a parasympathomimetic drug is invaluable. The choice of oral mecholyl in this case was based upon experimental observations, its prolonged action, ease of administration and low toxicity.^{6,13,16} The drug has also been used in the treatment of tabes dorsalis and congenital megacolon which, incidentally, may be associated with bladder paralysis.^{14,16} In our case the condition most recalcitrant to treatment was the persistent pyuria.

SUMMARY

The case of a thirty-three year old diabetic who presented the typical picture of diabetic neuropathy is reported. In addition to the more common neurologic signs and symptoms there were impaired intestinal motility, neurogenic bladder, impotence and orthostatic hypotension. Diabetic control had been poor over a period of many years. Emphasis is placed upon the early recognition and treatment of such conditions. A gratifying degree of clinical improvement was achieved in this case.

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American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE NATIONAL
MEETING HELD IN ATLANTIC CITY, MAY 4, 1948.

VARIATIONS IN COLONIC LYSOZYME PRODUCTION IN VARIOUS EMOTIONAL STATES. *William J. Grace, M.D. and Paul H. Seton, A.B., New York, New York.* (From the Departments of Medicine and Psychiatry of the New York Hospital and Cornell University Medical College.)

Lysozyme, a mucolytic enzyme described by Flemming in 1922, has been found by Meyer to occur in abnormally high concentrations in the stools of patients with chronic ulcerative colitis. He has produced acute ulcerative lesions in the upper gastrointestinal tract of dogs by feeding lysozyme and infers that it acts by destroying the protective mucous coating thus allowing for injury of the mucous membrane.

Our studies include the measurement of lysozyme in the stools of normal subjects, subjects with non-ulcerative diarrheas, those with ulcerative colitis in various stages of activity and the mucous secretions of a patient with ulcerative colitis who had a herniated, everted ascending colon on the surface of his abdomen. Day to day measurements were made and correlated with life situations, attitudes and feeling states.

Our findings indicate that life situations associated with emotions of hostility, resentment and guilt are accompanied by an increase in motility, vascularity and an increase in lysozyme production.

STUDY OF THE COMPARATIVE VALUE OF TETRAETHYLAMMONIUM BROMIDE AND SPINAL ANESTHESIA IN SELECTION OF HYPERTENSIVE PERSONS FOR SYMPATHECTOMY. *Louis A. Soloff, M.D. and (by invitation) W. Emory Burnett, M.D. and C. T. Bello, M.D., Philadelphia, Pennsylvania.* (From the Temple University Hospital.)

A comparison of the results of extensive thoracolumbar sympathectomy and gangliectomy with the preoperative responses to tetraethylammonium bromide and spinal anes-

thesia was made in an attempt to evaluate these two procedures as tests for the selection of hypertensive persons for sympathectomy.

There was no constant relationship of the magnitude and at times of the direction of the blood pressure changes due to the administration of tetraethylammonium bromide and that due to the production of diagnostic spinal anesthesia. In only 60 per cent of the patients was there a significant response of the blood pressure to both procedures. In some the response was greater to tetraethylammonium bromide and in others to spinal anesthesia. Significant blood pressure lowering effects due to either procedure or due to both were obtained in patients who had no postoperative blood pressure changes. Postoperative changes in blood pressure may be obtained in patients who have poor responses either to tetraethylammonium bromide or spinal anesthesia.

These procedures are not reliable in predicting the results of sympathectomy. With information available at the present time, it is advised that sympathectomy for hypertension should not be withheld on the basis of insignificant responses to tetraethylammonium bromide or spinal anesthesia.

RELATIONSHIP OF INITIAL LEVEL OF ANTIBODY TO MAGNITUDE OF ANTIBODY RESPONSE IN MAN. *Lowell A. Rantz, M.D., San Francisco, California.* (From the Department of Medicine, Stanford University School of Medicine.)

Immunologists have usually described serum antibody in terms of the geometric progression of dilution systems. When this has been done, the magnitude of a response stated as tube or fold increases has varied inversely with the initial concentration of antibody.

Analysis of the data derived from the immunologic study of a large number of cases of group A hemolytic streptococcus sore throat indicates that this technic for the expression

of the results of antibody titration has obscured certain important facts. The mean magnitude of the antistreptolysin "O" response was comparable regardless of the concentration of antibody present at the onset of the infection until the decrements of serum in the system became too great to permit the measurement of response within the limits of the expected absolute increase in circulating immune substance.

It was also demonstrated that the frequency of occurrence of "significant" "two tube" increases in antibody was a function of the initial level of antistreptolysin "O." Analysis of available published data indicates that these same principles apply to the antibody response following immunization of human beings with the viruses of influenza A and B.

These observations demonstrate that antibody concentration should be expressed in terms related to the actual amounts of these substances present in the serum and that the absolute magnitude of the increase should be one of the criteria used in the evaluation of immunization procedures and in the diagnosis of infection.

INFECTIOUSNESS AND INCUBATION PERIOD OF PRIMARY ATYPICAL PNEUMONIA. *William S. Jordon, M.D., Cleveland, Ohio.* (From the Departments of Preventive Medicine and Medicine, Western Reserve University, School of Medicine.)

Clinical and epidemiologic studies have provided relatively little information as to the degree of infectiousness and the incubation period of primary atypical pneumonia. Transmission experiments in human volunteers have demonstrated that this disease can be produced by direct inoculation of respiratory tract secretions. In those volunteers who developed primary atypical pneumonia the incubation periods varied from seven to eight days when untreated inoculum was used and from eight to fourteen days, with an average of twelve days, when filtered inoculum was used. The two inocula induced atypical pneumonia in 25 per cent and 29 per cent of cases, respectively.

During the past winter seventy-two cases of primary atypical pneumonia in adults have been observed at Lakeside Hospital. Of twenty-seven patients, representing twenty-four families, twenty-five gave a history of exposure to an

individual with an acute respiratory illness and two patients constituted index cases in a family outbreak of respiratory disease. In the twenty-four households acute respiratory illnesses variously diagnosed by private physicians as "severe colds," "bronchitis" or "virus pneumonia" occurred in forty-two additional persons, giving a total of sixty-nine respiratory infections in these families. Figures for total household memberships, including servants, were obtained for fifteen families and revealed that forty-nine of sixty-one individuals became ill, an attack rate of 80 per cent. Of these forty-nine patients twenty-three, or 47 per cent, were confirmed by roentgenologic and serologic studies. Two other sera were not diagnostic and we were unable to study the remaining twenty-four patients.

In twenty-one families with fifty-seven cases incubation periods from time of onset in the index cases were obtained in thirty-six instances. These periods ranged from five to nineteen days, with an average of 12.9 days.

These clinical and epidemiologic findings indicate that primary atypical pneumonia is indeed an infectious disease; it may in some instances have a high attack rate and it has an incubation period comparable with that of the experimentally transmitted disease.

TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH MASSIVE DOSES OF PENICILLIN SYSTEMICALLY. *Harry F. Dowling, M.D., H. J. Hirsch, M.D. and (by invitation) L. K. Sweet, M.D., W. W. Zeller, M.D. and J. A. Robinson, M.D., Washington, D. C.* (From the George Washington University Medical Division, Gallinger Municipal Hospital.)

When penicillin is employed in addition to sulfonamides in the treatment of pneumococcic meningitis, the case fatality rate is reduced materially below that obtained with the use of sulfonamides alone. Among the forty patients treated in this hospital with sulfonamides alone, 93 per cent died while only 62 per cent died among sixty-six patients who received a combination of sulfonamides and penicillin systemically plus repeated intrathecal injections of penicillin. The latter method is the one which is widely used at present and consists of penicillin intrathecally in doses of 10,000 to 20,000 units of penicillin at twelve to twenty-four-hour

intervals as well as 200,000 to 500,000 units systemically during each twenty-four-hour period. Full doses of sulfadiazine or sulfamerazine are given concomitantly.

This regimen is not without many dangers however. Intrathecal injections may cause myelitis or radiculitis and intraventricular instillations may result in convulsions. Irritation of the meninges produces pleocytosis and adhesions and may result in spinal fluid block. Secondary injections are sometimes introduced when repeated lumbar punctures are done. Additional dangers are the time consumed in performing so many lumbar punctures and the annoyance to the patient which they entail.

Intrathecal instillations of penicillin continue to be employed because a number of investigators have been unable to detect penicillin in therapeutic quantities in the cerebrospinal fluid after administering it systemically. Previous studies done in our laboratory convinced us that several factors were important in obtaining and maintaining a satisfactory concentration of penicillin in the cerebrospinal fluid: (1) sufficiently large amounts of penicillin must be administered systemically; (2) the penicillin must be administered for a long enough time and (3) penicillin diffuses into the cerebrospinal fluid more freely in the presence of inflammation. When Schwemlein and his associates reported that therapeutic concentrations of penicillin could be consistently obtained in patients receiving 20,000,000 units or more during a twenty-four-hour period by continuous intravenous drip, we decided to treat all of our patients with pneumococcic meningitis with large doses of penicillin systemically. Nineteen patients have been treated in this manner up to the present time. A dose of 1,000,000 units intramuscularly every two hours was agreed upon. Spinal fluid penicillin concentrations were determined in fourteen subjects with and without meningitis. Penicillin was detectable in the spinal fluids of all of these subjects and was consistently present in every specimen obtained after the twelfth hour of treatment. Twelve of the patients except one were given sulfonamides and in addition three patients were given a single intrathecal dose of penicillin.

RATE OF MOVEMENT OF FLUID FROM VASCULAR TO EXTRAVASCULAR SPACES DURING A SYSTEMIC RISE OF VENOUS PRESSURE IN MAN. *Ellen Brown, M.D., and (by invita-*

tion) James J. Hopper, Jr., M.D., Charles Mudrick, M.D. and John J. Sampson, M.D., San Francisco California. (From the Division of Medicine of the University of California Medical School.)

Experiments were conducted to determine the effect of a systemic increase of venous pressure on movement of fluid between vascular and extravascular spaces in man. Normal subjects performed Valsalva maneuvers twice per minute for thirty minutes, resting one minute of five while blood samples were collected. Antecubital venous pressure was measured at five-second intervals by a water manometer. The overall change of venous pressure from the resting level was estimated planimetrically. Initial plasma volume was measured with T-1824. By comparison of hematocrits and protein concentrations of venous blood collected at intervals during efforts and recovery with those obtained initially, fluid movements and approximate protein concentration of the capillary filtrate could be calculated. Correction was made for the introduction of measured volumes of heparinized saline (totaling 100 to 160 cc.) required to prevent coagulation in collecting needle and manometer.

In ten experiments on six subjects overall increases of venous pressure were between 10.4 and 20.8 cm. water. Filtration occurred rapidly at first and became progressively slower. Total volumes of fluid filtered were between 184 and 680 cc., representing 4.2 to 11.0 per cent of initial blood volume. Unit rates of filtration (cc. of fluid lost per min. per Kg. body weight per cm. increase of venous pressure) were between .020 and .040 for the first nine and one-half minutes and between .010 and .024 for twenty-nine and one-half minutes of effort. While the observed unit rates for nine and one-half-minute periods were in close agreement with unit rates of filtration during local congestion of the human forearm obtained by others using different technics, the unit rates observed here for twenty-nine and one-half-minute periods were far smaller, suggesting that other factors beside rising tissue pressure were acting to conserve blood volume. In these experiments losses of fluid and protein must have occurred in trunk and extremities only because abdominal and thoracic organs were supported by pressures equivalent to the increase of venous pressure.

STUDIES ON THE MECHANISM OF REDUCTION IN RENAL FLOW IN HEART FAILURE. PRELIMINARY REPORT. *Haywood Turner, M.D.* and (by invitation) *David F. James, M.D.* and *Arthur J. Merrill, M.D.*, Atlanta, Georgia. (From the Departments of Medicine and Physiology, Emory University School of Medicine.)

A striking reduction in renal plasma flow and filtration rate has been found in severe heart failure and is probably important in the retention of salt and water which occurs. These changes are out of proportion to the reduction in cardiac output. They appear to be due to constriction of the efferent arteriole of the kidney since the filtration rate is maintained at a relatively normal level until the renal plasma flow falls to around 200 cc. per minute. This renal vasoconstriction could be due to sympathetic stimulation or to a humoral substance. The purpose of this paper is to evaluate the rôle of the sympathetic nervous system in this phenomenon.

Since the changes in renal circulation have been shown to be related to the inadequacy of cardiac output rather than to venous pressure, a procedure which produces a reduction in cardiac output was carried out in two individuals with loss of function of the sympathetic nervous system. Tilting of a motionless normal individual to the upright position produces an average fall in cardiac output of about 20 per cent, associated with a 30 to 60 per cent fall in renal plasma flow. One sympathectomized subject and one subject with orthostatic hypotension had falls in renal plasma flow and filtration rates similar to those of normal individuals; this occurred although the blood pressure did not drop.

Spinal anesthesia was administered to three patients with heart failure and reduction in renal blood flow. Although this was carried to a level above the sympathetic nerve supply to the kidney, no increase in blood flow resulted. This could have been due to inability of the kidney to increase its flow after long-standing vasoconstriction. This seems unlikely because the depressed renal blood flow of three thyrocardiac patients returned to normal after successful treatment of the thyrotoxicosis. Seven subjects with decreased renal blood flow from congestive failure were given aminophylline

with remarkable increases in cardiac output and a considerable increase in renal blood flow although the latter did not return to normal.

The above data suggest that the sympathetic nervous system is not implicated in the renal shutdown in heart failure and point to a hormonal regulation. One patient with long-standing Addison's disease who was well controlled as to blood volume and blood pressure showed a change in renal function similar to that in heart failure.

CIRCULATORY AND RENAL EFFECTS OF AMINOPHYLLINE IN CONGESTIVE HEART FAILURE. *David F. James, M.D.* and (by invitation) *Haywood Turner, M.D.*, and *Arthur J. Merrill, M.D.*, Atlanta, Georgia. (From the Departments of Medicine and Physiology, Emory University School of Medicine.)

The effects of aminophylline on patients with congestive heart failure have been studied by the simultaneous observation of the cardiac output, right atrial, pulmonary arterial and systemic arterial pressures, glomerular filtration rate, renal plasma flow and sodium excretion data. These patients were suffering from valvular heart disease and showed no evidence of primary renal disease. Aminophylline injected intravenously in 0.72 Gm. doses has been found to produce a marked increase in cardiac output, accompanied by a decrease in peripheral resistance, which is of greater degree in the pulmonary than in the systemic circulation. The fall in right atrial pressure reported by McMichael et al. to occur after aminophylline administration in such patients was also noted by us.

Increased renal plasma flow, filtration rate and an increased rejection of sodium by the tubules also took place. These renal changes are minor in degree, however, and not of an order comparable to the modification in cardiac output (which at times is nearly tripled).

The impressive diminution in pulmonary arterial pressure (in some cases as much as 20 mm. Hg mean pressure) is an expression of a lessening of the pulmonary resistance. Whether this is due to a direct action of aminophylline on the pulmonary vascular bed or is a secondary effect of improved left ventricular contraction is not known.

SOME REASONS FOR FAILURE IN USE OF DICUMAROL IN TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION. *Charles D. Marple, M.D. (by invitation) and Irving S. Wright, M.D., New York, New York.* (From the New York Hospital and the Department of Medicine, Cornell University Medical College.)

The anticoagulants, dicumarol and heparin, are used widely in the prevention and treatment of thromboembolic complications. To evaluate the use of dicumarol in the treatment of coronary thrombosis with myocardial infarction sixteen hospitals have observed one thousand patients with coronary occlusion treated similarly except that approximately one-half the patients received dicumarol in addition to conventional therapy. Dicumarol was administered usually in doses of 300 mg. the first day, 200 mg. the second day and 100 to 200 mg. on each successive day on which the prothrombin clotting time of whole plasma fell below thirty seconds as measured by the Link-Shapiro modification of the Quick one-stage technic. Heparin was administered to approximately one-sixth of the treated patients for the first few days, ordinarily in doses of 50 mg. every four hours. The following statements are based upon preliminary analysis of this material:

Failures of dicumarol therapy resulting in thromboembolic complications with or without death may occur under the following circumstances: (1) During the initiation of dicumarol therapy since significant prolongation of the prothrombin clotting time does not occur from forty-eight to seventy-two hours after administration of an adequate initial dose of dicumarol. To prevent thromboembolic complications during this period it is necessary to administer heparin concurrently and in adequate doses. (2) During the initiation of dicumarol therapy when the simultaneous administration of heparin has been discontinued arbitrarily before the prothrombin clotting time has reached an adequate level, ordinarily thirty to forty seconds. Thromboembolic complications may then occur in the interval during which neither drug is therapeutically effective. (3) When, during the course of dicumarol therapy, the prothrombin clotting time is permitted to fall below a therapeutic level. (4) When dicumarol therapy is discontinued prematurely while the hazard of thromboembolic phenomena still exists.

Hemorrhagic complications of dicumarol therapy, while infrequent and rarely severe in this series, may be anticipated in the following circumstances: (1) When the prothrombin clotting time is excessively prolonged. Bleeding is more apt to occur when the prothrombin clotting time of whole plasma is permitted to exceed sixty to seventy seconds. (2) In the presence of hepatic or renal disease when the response to dicumarol may be exaggerated and the prothrombin level may fluctuate widely. (3) In the presence of renal disease, hemorrhagic diathesis, or open lesion (e.g., peptic ulcer) when bleeding may occur at relatively normal prothrombin levels.

Ordinarily, bleeding resulting from dicumarol administration is promptly and effectively controlled by the injection of synthetic vitamin K preparations in doses of 60 to 75 mg. or by transfusions of whole blood.

There is marked variation in the response of individual patients to dicumarol and each subject must be handled as an individual problem. Some patients will tolerate excessively elevated prothrombin clotting times for a considerable period of time without bleeding. In our experience excellent therapeutic results and almost no hemorrhages have occurred when the prothrombin clotting time is maintained between thirty and forty seconds.

Dicumarol appears to reduce significantly the incidence of thromboembolic complications following coronary occlusion with myocardial infarction and does not present serious danger of hemorrhage if administered under careful supervision and adequate laboratory control.

INTRAVENOUS AORTOGRAPHY AND NEPHROGRAPHY. *H. S. Weens, M.D. and (by invitation) H. M. Olnick, M.D., D. F. James, M.D. and J. V. Warren, M.D., Atlanta, Georgia.* (From the Departments of Roentgenology, Medicine and Physiology, Emory University School of Medicine.)

It has been found that the human kidney parenchyma, as well as the abdominal aorta and its branches, may be opacified and visualized roentgenologically following rapid intravenous injection of 50 ml. of 70 per cent diodrast solution. The technic of injection is similar to that described by Robb and Steinberg for contrast visualization of the heart and large vessels

(angiocardiology), utilizing an antecubital vein as the site of injection. Serial roentgenograms of the abdomen in the supine position are obtained with the aid of a rapid cassette changer and a self-reecking bucky diaphragm.

Thirty patients have been studied. Beginning opacification of the abdominal aorta and its branches was usually observed eight to twelve seconds following termination of the rapid intravenous injection. Four to six seconds later maximal opacification of the kidney parenchyma (nephrogram) occurred, permitting a clear differentiation of the kidney shadows from surrounding structures. In many instances, the renal cortex, medulla and hilus were distinctly defined.

The results obtained compare favorably with those obtained by direct injection of the aorta. Although visualization of the aorta and its branches as described here does not attain the degree of radiologic contrast observed following aortic injection, it has the following advantages: greater ease of injection, utilization of a contrast medium safer than the sodium iodide used for direct aortography and ability to perform the procedure without special apparatus or anesthesia.

This method may be utilized not only in the study of renal circulation but also in the differential diagnosis of renal and extrarenal masses.

INTRATHECAL EPHEDRINE SULFATE ANESTHESIA IN OBSTETRICS. *W. Robert Penman, M.D., Philadelphia, Pa.* (From the Department of Obstetrics and Gynecology of the Temple University School of Medicine and Hospital.)

In the Department of Obstetrics and Gynecology ephedrine sulfate has been used to produce spinal anesthesia for delivery. When the patient is ready for delivery, she is placed on her side and the skin over the lumbar spine is prepared and sterile drapes applied. A spinal puncture is made with a spinal needle in the fourth lumbar interspace and when a free flow of spinal fluid is obtained, the anesthetic mixture is injected slowly during the intervals between uterine contractions. In this group of patients 2 ml. of a solution containing 50 mg. ephedrine sulfate and 5 per cent dextrose has been used. Following the injection, the patient is placed in the dorsal position without a pillow for a period of three to five minutes after which the

table is elevated 15 degrees to aid in low fixation of the anesthetic agent.

With this technic, anesthesia adequate for delivery has been obtained in 95.4 per cent of twenty-two cases. The sensory anesthetic level rises to T-10 to T-11 and is maintained for at least sixty minutes. Motor function of the uterus and lower extremities is unaltered.

No untoward maternal complications attributable to the ephedrine sulfate injection have been observed. Likewise, fetal physiology is apparently not disturbed as evidenced by the fact that there has been no change in the fetal heart rate between the time of injection and delivery nor is there any fetal respiratory depression after delivery. At this time it appears that intraspinal ephedrine sulfate is a satisfactory anesthetic agent for spontaneous or low forceps delivery of normal patients and for the performance and repair of episiotomies.

EFFECT OF SEDATIVES ON URINARY VOLUME OF PREGNANT WOMEN. *Willis E. Brown, M.D., Otto F. Kraushaar, M.D. and (by invitation) J. T. Bradbury, Sc.D. and Y. K. Wang, M.D., Iowa City, Iowa.* (From the University of Iowa College of Medicine.)

In a previous communication before the Midwestern Section of this Society we have reported the effectiveness of diuretic agents in the mobilization and excretion of sodium and water. This study deals with the effect of sedatives and their antidiuretic effect.

A series of patients were given a constant intravenous infusion for five hours and hourly urine specimens were obtained for eight hours. On test days these patients were given injections of a sedative and the effect on the urinary output and chloride excretion was measured. Morphine reduced the urinary output by 50 per cent without any significant alteration in urinary chlorides. When the patient was hydrated by oral administration of fluids, morphine, demerol, codeine and amytal caused a depression in urinary volume. Paraldehyde and avertin have not been found to have an antidiuretic effect.

Additional studies were undertaken to determine the mechanism of the antidiuretic effect of morphine. By detailed studies on normal subjects and patients with diabetes insipidus it appears that this effect is not mediated by the posterior pituitary.

IMPORTANCE OF SERUM POTASSIUM IN THE SYNDROME OF HYPOPOTASSEMIA AND ITS INFLUENCE ON ELECTROCARDIOGRAMS IN PATIENTS WITH DIABETIC ACIDOSIS, *Carl S. Nadler, M.D., Samuel Bellet, M.D., and Mary Lanning, B.S., Philadelphia, Pennsylvania.* (From the Philadelphia General Hospital.)

This report is based upon the changes in the electrolytes, especially potassium, which occurred before and during the treatment of forty-five patients with diabetic acidosis and the relation of these changes to their electrocardiograms.

In every patient studied the serum potassium level was found to be elevated or normal before treatment and fell to levels below normal after institution of therapy. Signs of hypopotassemia became evident during the period of three to eighteen hours after the first administration of insulin and did not necessarily parallel the severity of the acidosis. The pH of the blood showed the best correlation with the serum potassium. The carbon dioxide combining power, cation and anion concentrations, and amounts of insulin, fluids and glucose administered showed a lesser degree of correlation.

Changes in the duration of electrical systole, alterations in the amplitude of the T wave and the presence or absence of a U wave in the electrocardiogram were found to provide a reliable guide in forming an approximate estimation of the serum potassium level. Statistical correlation of these electrocardiographic changes with the electrolytic concentrations of the serum furnished strong evidence that these electrocardiographic findings and certain clinical symptoms were governed for the most part by the serum potassium level. Studies of the effects of intravenous potassium chloride add further evidence to the validity of these observations.

DISTRIBUTION OF POTASSIUM BETWEEN SERUM AND CERTAIN EXTRACELLULAR FLUIDS IN MAN. *B. P. Folk, M.D., K. L. Zierler, M.D., and J. L. Lilienthal, Jr. M.D., Baltimore, Maryland.*

In the course of studies on the effect of various concentrations of $[K^+]$ on excitable tissues it became necessary to estimate the $[K^+]$ in interstitial fluid surrounding muscle cells. In-

direct estimates could be made best by determining the $[K^+]$ in serum. A review of published data revealed that the ratios of concentration in serum water and extracellular fluid water (R_{st}) for Na^+ , Cl^- and HCO_3^- indicated free diffusibility within the limits of the Gibbs-Donnan equilibrium. (R_{st}) for $[K^+]$, however, suggested that a significant but highly variable amount of $[K^+]$ in serum was inactive. The reported (R_{st}) for $[K^+]$ varied from 0.40 to 1.00 in the fifty-three reported studies. The average values have risen steadily since 1922 from 0.60 to 0.84 in 1934.

We have restudied the distribution of $[K^+]$ and Na^+ between serum and extracellular fluids (pleural, peritoneal and subcutaneous) in twenty-two instances in man. Analyses were made on serum (separated from cells by immediate centrifugation and recentrifugation) and on fluids by a modified Berry-Chappell-Barnes internal standard flame photometer which afforded a high degree of reproducibility and an error on recovery from biologic fluids not exceeding 2 per cent. The average (R_{st}) for $[K^+]$ was 0.92 (range 0.82 to 1.03) and for Na^+ 0.96 (0.91 to 1.00).

This small difference might well result from leakage of $[K^+]$ from erythrocytes to serum occurring prior to separation. Theoretical calculations indicate that the loss of but 0.2 per cent of intraerythrocytic $[K^+]$ to serum will account for a drop in (R_{st}) from 0.96 to 0.92. Indirect support for this supposition is afforded by the observation that in the dog, in which intraerythrocytic base is predominantly Na^+ , the (R_{st}) for $[K^+]$ is 0.94.

On the basis of these observations it is concluded that $[K^+]$ diffuses freely between blood and interstitial fluid. If "binding" by serum proteins exists, it would appear to be insignificant in extent.

HYALURONIDASE AND HYALURONIDASE INHIBITORS IN BODY FLUIDS IN NORMAL AND DISEASE STATES. *John K. Fulton, M.D., Stanley Marcus, Ph.D. and W. D. Robinson, M.D., Ann Arbor, Michigan.*

The ability of hyaluronidase to decapsulate a group c streptococcus has been standardized to permit quantitative estimation of the enzyme and to test for enzyme inhibition. The technic is capable of detecting concentrations as low as 0.01 viscosity reducing unit per cc. By this

method various body fluids in rheumatic fever, rheumatoid arthritis, pemphigus, carcinoma and in normal persons have been tested for the presence of enzyme or enzyme inhibitors. No significant alteration from the normal was found in any of these diseases except carcinomatosis when enzyme inhibition occasionally is very marked but not consistent from patient to patient. Hyaluronidase could not be demonstrated in serum of rheumatic fever, serum and joint fluid of rheumatoid arthritis nor in the serum and bullae fluid of pemphigus. Hyaluronidase is not demonstrable in sterile, fresh unextracted urine of normal or cancer patients. Salicylate, gold and PABA exert no *in vitro* inhibition of hyaluronidase in therapeutic concentrations. Urine and serum of persons taking salicylates do not contain more inhibitor substance than controls. The natural serum constituent responsible for hyaluronidase inhibition is thermolabile and appears to vary considerably in normal subjects. The mechanism of its occasional marked increase in carcinomatosis is not known.

OBSERVATIONS ON ELECTROLYTE METABOLISM IN ADDISON'S DISEASE AND GASTRIC CANCER. *Aurelia Potor, M.D., Nelson F. Young, Ph.D., F. Homburger, M.D. and Edward C. Reifstein, Jr., M.D., New York, New York.* (From the Department of Clinical Investigation, The Sloan-Kettering Institute for Cancer Research Memorial Hospital Center for Cancer and Allied Diseases.)

The studies presented are the result of an inquiry into the metabolic alterations associated with neoplastic disease and the rôle of the adrenal cortex in these aberrations.

The investigation consisted of total electrolyte balance studies for a period of ten to twelve days and analysis of tissue electrolytes. In each instance sodium chloride was administered in progressively increasing amounts in constant daily increments, reaching a level of approximately 1,000 mEq. a day.

Linear representation of urinary excretion of sodium in the individuals studied permitted comparison of slopes of intake and urinary output. The resulting quotients were: normal, 0.98; Addison's disease, 0.3; gastric cancer, 0.6 to 0.75. Electrolyte distribution in tissue

removed at termination of the period of large sodium chloride intake indicated a pronounced increase in sodium and chloride content and a slight decrease in potassium content of muscle from both Addison's disease and gastric cancer as compared with the electrolyte content of muscle from the normal subject.

CHANGES IN SODIUM EXCRETION IN PATIENTS WITH CIRRHOSIS OF THE LIVER FOLLOWING INTRAVENOUS ADMINISTRATION OF ALBUMIN, MERCURIAL DIURETICS AND A LOW SODIUM DIET. *William W. Faloona, M.D. (by invitation), Richard D. Eckhardt, M.D., Arnold N. Cooper, M.D. (by invitation) and Charles S. Davidson, M.D., Boston, Massachusetts.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.)

Repeated intravenous administration of salt-poor human albumin to twenty patients with cirrhosis of the liver led to improvement of edema and ascites in only thirteen. Failure to find a correlation between serum albumin concentration and delivery of retained fluid led to a study of other factors, especially the rôle of sodium, in fluid retention.

Diuresis with loss of ascites and edema in one patient given a 91 mEq. sodium diet promptly followed administration of albumin. Sodium excretion rose from 10 mEq. daily in the pre-diuresis period to 156 mEq. although the serum albumin concentration rose but slightly. Another patient similarly treated on a 123 mEq. sodium diet increased his sodium excretion from control 5 mEq. daily but to only 40 mEq. daily with little effect upon ascites and edema although albumin concentration rose to almost normal.

In spite of a serum albumin concentration maintained above 3.5 Gm. per cent by repeated injections of albumin two patients retained sodium, increased their ascites and gained weight while receiving a constant diet containing 123 mEq. of sodium daily. When the sodium intake was reduced to 21 mEq. daily, the rate of weight gain and ascites formation was markedly diminished and approximate sodium equilibrium was achieved.

Following the administration of mercurial diuretics, three patients with a dietary sodium of 21 mEq. daily showed a 6 to 10-fold increase in urinary sodium excretion and a consistent weight loss without change in serum-albumin concentration. In a patient undergoing spontaneous improvement in ascites and edema after eight months of albumin therapy excretion of sodium was found to be normal and an intake of sodium as high as 250 mEq. daily did not cause weight gain.

It is concluded that accumulation of ascites and edema in cirrhosis is primarily due to diminished ability to excrete sodium. This may be partially overcome by administration of albumin or mercurial diuretics and prevented, in part, by use of a low sodium diet.

EFFECT OF CARONAMIDE AND HEPARIN ON THE COAGULATION TIME OF HUMAN BLOOD.

Howard Sirak, M.D. and (by invitation) Curtis P. Artz, M.D., Columbus, Ohio.
(From the Department of Surgery, the Ohio State University College of Medicine.)

Papers previously written on caronamide have been concerned with its use in enhancing penicillin blood levels. Apparently, 4' carboxy-phenylonethanesulfonamide (caronamide) produces this effect by inhibiting the excretion of penicillin by competing for the renal enzyme transport mechanism. Caronamide, which has a very low index of toxicity, produces a similar effect upon para-aminobenzoic acid, diodrast and other compounds totally unrelated structurally. It was hoped that caronamide might cause a similar prolongation or enhancement of the heparin effect upon coagulation, thereby reducing the cost and facilitating the administration of heparin.

Ten patients were selected for the first part of this study. The effect of caronamide and heparin in saline was determined as follows: A control heparin tolerance test was performed on the first day. On the second day a single oral 4 Gm. dose of caronamide was given. No further caronamide was administered throughout the experiment. The heparin tolerance test was then started one-half hour later and repeated on subsequent days.

This resulted in a gradual progressive enhancement of heparin effect for the first two days, a sharp peaking on the third or fourth day

and then a gradual decline to control levels by the sixth or seventh day following caronamide administration. The "twenty-minute" blood sample always demonstrated the greatest enhancement. In eight of ten cases the prolongation of the coagulation time of this sample (at the peak period) was two to ten times greater than the corresponding sample of the pre-caronamide control period. Heparin levels performed simultaneously bore no correlation to the coagulation times.

In the second part of the study, using heparin in gelatin menstruum, caronamide demonstrated its effectiveness in reducing, approximately by one-half, the amount of heparin in gelatin menstruum needed to maintain a therapeutic elevation of the coagulation curve. This effect was achieved by using a combination of caronamide and heparin/saline injected intravenously as a priming dose, plus multiple oral doses of caronamide. The priming dose was injected. After an interval it was followed by heparin/gelatin and the first of the multiple doses of oral caronamide.

The result was a marked enhancement of the coagulation times of the heparin/gelatin curves. A quantity of heparin/gelatin produced no appreciable effect on the coagulation time; however, this same quantity, when combined with caronamide, effected a marked enhancement of the coagulation time into and beyond therapeutic levels.

EFFECT OF A PTEROYLGLUTAMIC ACID INHIBITOR IN LEUKEMIA AND RELATED DISORDERS. *Rosalie B. Neligh, M.D., Frank H. Bethell, M.D. (by invitation) and Muriel C. Meyers, M.D., Ann Arbor, Michigan.*

Fourteen patients with leukemia and related disorders were treated with a pteroylglutamic acid inhibitor (4-amino pteroylglutamic acid). The cases included three of acute or subacute myelogenous leukemia, three of early and two of advanced chronic myelogenous leukemia, two of chronic lymphocytic leukemia, two of leukemic lymphosarcoma, one of monocytic leukemia and one of multiple myeloma.

The material, which was not a pure compound, was given either orally or parenterally in daily doses ranging between 2.5 mg. and 30 mg. The most consistent finding was a decrease in the total granulocyte count which became apparent from three to fourteen days after the

start of the treatment, usually without a significant change in the differential count. Changes in erythrocyte and platelet values were variable but prolonged administration of the larger doses appeared to depress the formation of these elements. Sternal marrow aspirations revealed a progressive decrease in myeloid activity affecting chiefly, but not exclusively, the granulopoietic elements.

In some patients with myelogenous leukemia, splenomegaly decreased and symptoms of hypermetabolism subsided during therapy. On its discontinuance increased activity of the leukemia process rapidly recurred. Observations on one patient indicate that reversibility of the effect of the inhibitor by simultaneous administration of pteroylglutamic acid may be produced.

The course of the disease in the advanced or acute cases was not materially influenced by administration of 4-amino pteroylglutamic acid. Whether or not the compound will have practical value in the management of suitable cases of chronic leukemia remains to be determined. Early experiences indicate that 4-amino compound and other structural analogues of folic acid may be of importance in the study of the growth requirements of both normal and leukemic tissue.

RECENT CLINICAL STUDIES WITH PARA-AMINOBENZOIC ACID. *Chris J. D. Zaranfonetis, M.D. (introduced by Sibley W. Hoobler, M.D.), Ann Arbor, Michigan.*

Para-aminobenzoic acid in the form of sodium para-amino-benzoate (NaPAB) was administered in large doses to thirteen patients with leukemia. Six patients with chronic myelogenous leukemia had a definite decline in their white cell count. Transient clinical improvement was observed in some of these patients. Upon discontinuation of the drug, the leukocyte count increased. It was impossible to evaluate the effects of NaPAB in the seven patients who had other forms of leukemia. NaPAB appeared to exert an inhibitory effect on all phases of granulocyte development. No specific alterations in differential counts were attributable to its action. Vacuolation appeared in the myeloblasts and promyelocytes during treatment.

In ten of eleven patients with lupus erythematosus there was improvement in the skin lesions following administration of NaPAB. Improvement was most marked in patients who

exhibited photosensitivity and had "active" lesions associated with burning and/or itching. During treatment such lesions showed gradual fading of erythema and diminution of infiltration and edema. After NaPAB therapy was discontinued the lesions usually reappeared. In three patients the lesions again regressed upon resumption of NaPAB therapy.

Similarly, administration of NaPAB to three patients with dermatitis herpetiformis and to two patients with active dermatomyositis resulted in objective improvement.

Renal glycosuria occurred during NaPAB therapy. Dermatitis medicamentosa was encountered once.

It is emphasized that NaPAB is not a cure for these varied conditions of unknown etiology. These findings, however, along with previous observations, indicate a broad range of physiologic activity for this compound.

RAPID SLIDE TEST FOR HETEROPHILE ANTIBODIES IN INFECTIOUS MONONUCLEOSIS. *W. G. Moloney, M.D. and (by invitation) L. Malzone, M.D., Boston, Massachusetts. (From the Clinical Research Laboratory, Holy Ghost Hospital, and the Medical Department Tufts Medical School.)*

Several investigators have postulated the presence of blocking or incomplete antibody in the sera of patients with infectious mononucleosis. For the past three years studies have been carried out in a large group of individuals employing a slide technic modified after Diamond's test for Rh antibodies.

The test is carried out by mixing defibrinated or citrated sheep's blood (0.1 cc.) with serum to be tested (0.2 cc.) on a glass slide. Tests were considered positive only if 3 plus to 4 plus macroscopic clumping occurred within thirty to sixty seconds. Sera were also examined by the Paul-Bunnell test and a serum dilution of 1:112 was the lowest considered a positive reaction.

Of the 407 individuals studied very few positive tests were encountered except in infectious mononucleosis. (Table 1.) The nature of the agglutinin in the three cases of cirrhosis and the one case of myeloma was not determined. The positive slide tests found in infectious mononucleosis, with one exception, occurred only when the saline agglutinating heterophile antibody was present in a diagnostic serum dilution level. There has been little evidence thus far

in this study for the presence of incomplete or blocking antibody for sheep cells in infectious mononucleosis.

As a practical test the slide method seems to be a rapid and useful procedure in the diagnosis of infectious mononucleosis.

TABLE I
RESULTS OF ANTIBODY STUDIES ON THE SERA OF
407 INDIVIDUALS

Diagnosis	No. Cases	Positive Slide Test	Positive Paul-Bunnell Test
Infectious mononucleosis	29	29	29
Infectious mononucleosis*	6	1	0
Infectious hepatitis	17	0	0
Cirrhosis of the liver	24	3	0
Pregnancy	95	0	0
Malignancy	30	0	0
Cord blood	23	0	0
Myeloma	2	1	0
Acute hemolytic Anemia	6	2†	0
Iso-immune anti-Rh	10	0	0
Iso-immune anti-A ₁	2	0	0
Iso-immune anti-A ₂	1	1	1
Iso-immune anti-B	1	0	0
Miscellaneous diseases	50	0	0
Controls	110	0	0

* These cases were clinically and hematologically typical of infectious mononucleosis.

† Tests were negative when carried out at 37°C. by the slide method.

NITROGENOUS CONSTITUENTS OF THE URINE FOLLOWING SEVERE BURNS.* *Kendall Emerson, Jr. M.D.* and (by invitation) *Otto F. Binkley, M.D., Boston, Massachusetts.* (From the U. S. Naval Medical Research Unit No. 2.)

Two patients were studied following first and second degree burns involving 60 and 40 per cent of their body surface, respectively. The daily urinary excretion of total nitrogen, urea plus ammonia nitrogen, alpha amino nitrogen by the ninhydrin method and total amino nitrogen after hydrolysis by the nitrous acid method was measured. During the first ten days following the burns these patients excreted a daily average, respectively, of 26.88 and 13.69

* The Bureau of Medicine and Surgery of the Navy does not necessarily endorse the views or opinions which are expressed in this paper.

Gm. of nitrogen. This included 22.65 and 12.03 Gm. urea plus ammonia nitrogen, 0.638 and 0.310 Gm. alpha amino acid nitrogen and 3.53 and 1.90 Gm. total amino nitrogen. The nitrogen excretion remained constantly elevated throughout the febrile period following the burn and showed no correlation with the nitrogen intake which was varied from 5.60 to 53.75 Gm. per day. Twenty Gm. of a synthetic mixture of the ten essential amino acids administered daily by vein for five to seven days during periods of low protein intake failed to affect the urinary nitrogen excretion except to increase the output of alpha amino nitrogen by approximately 0.25 Gm. per day, equivalent to 8 per cent of the amount administered. In spite of this both patients showed a rapid rise of plasma protein concentration during amino acid administration while they were still febrile and in negative nitrogen balance.

Total amino nitrogen in the urine remained elevated for approximately three weeks in both patients whereas urinary alpha amino nitrogen returned to normal in ten days or less. It is suggested that the increase of urinary amino nitrogen represents incomplete or abnormal protein breakdown products absorbed from the injured areas.

PHOTOMICROGRAPHS OF HUMAN CARCINOMA TAKEN WITH THE POLAROID COLOR-TRANSLATION ULTRAVIOLET MICROSCOPE.* *Robert C. Mellors, M.D., New York, New York.* (From the Sloan-Kettering Institute for Cancer Research, Memorial Hospital.)

Many objects not apparent in visible light are discernible in ultraviolet light because of inherent differences in ultraviolet absorption. This was recognized by Köhler who in 1904 described the first ultraviolet microscope. Indeed, the method described by Köhler and at a later date brilliantly extended by Caspersson depends upon the characteristic ultraviolet absorption of the nucleic acids which are prominent chemical constituents of chromosomes and other cell structures.

* This work was done in part under a Fellowship Grant of the American Cancer Society recommended by the Committee on Growth of the National Research Council and under contract with the Office of Naval Research, in cooperation with the Sloan-Kettering Institute.

The human eye constitutes a discriminately sensitive visual spectrophotometer. If ultraviolet absorption in the cell could be translated quantitatively in terms of visible light absorption, then the visual mechanism could be employed. At a glance the color translation method should reveal differences in ultraviolet absorption which otherwise could be shown only by time-consuming microphotometry. Such a principle was first formulated by the Russian scientist, Brumberg, in 1939. In this country the polaroid research group has worked for nearly a year on the technic of color-translation ultraviolet microscopy and on the development of better ways of examining fixed and living cells.

A preliminary study has been made of tissue

sections, smears and cells in tissue culture. Photomicrographs have been taken with the polaroid design reflecting ultraviolet objectives each at three wavelengths: 260, 280 and 300 $\mu\mu$, respectively. The three black and white negatives which serve as color separation negatives for the three primary colors are then translated into full color by the polacolor process. The results may be summarized as follows: The color-translation ultraviolet photomicrographs are comparable in appearance to tissue sections stained with a polychrome dye. At the state of our present knowledge, however, the analysis of the color differences between various cytologic and histologic components in terms of chemical differences cannot be put forth.

Book Reviews

A Manual of Pharmacology. By Torald Sollmann. 7th ed., 1132 pp. Philadelphia, 1948. W. B. Saunders Company. Price \$11.50.

The comprehensive and meticulous discussions, exhaustive documentation, and conscientious attention to recent advances which characterized previous editions extend to the seventh edition. The bibliography of this volume is very extensive despite the fact that the author has drawn mainly from the literature of the past twenty years. Drugs of recent interest, such as BAL, bacitracin, ANTU, folic acid, nitrogen mustards, antihistaminics and anticholinesterases are discussed as fully as available data permit. Reading is facilitated by a two-column format.

The vast scope of this work introduces problems in arrangement and selection which are not always solved successfully. There sometimes seems to be a lack of consistency in the order in which various aspects of the pharmacology of various drugs are considered; and occasionally it is not clear why certain topics have been assigned greater or lesser importance by relegating them to larger or smaller type. A paucity of structural formulas and illustrative charts and diagrams sometimes deprives the presentations of incisiveness.

In the opinion of the reviewer this book constitutes an invaluable reference manual for persons actively working in pharmacology or allied fields. The deficiencies in

presentation of subject matter somewhat impair its usefulness as a teaching textbook.

I.A.C.

The Engrammes of Psychiatry. By J. M. Nielsen, M.D. and George N. Thompson, M.D. Pp. 509. Springfield, Ill., 1947. Charles C. Thomas. Price \$6.75.

The authors have prescribed a book which is an attempt to put psychiatry in the same anatomic and localizing plane as neurology. They try to localize such mental functions as conation, consciousness, awareness, etc., in specific areas of the brain. The evidence given is certainly inconclusive and not scientific.

In the Psychoneuroses, the authors suggest the probability of an "underlying psychopathological mechanism" and the ability to find this depends upon the skill of the examining person. Although the mechanisms may be Freudian, the authors themselves do not seem convinced and hence certainly make no convincing impression upon the reader.

Psychopathic personality, schizophrenia and manic depressive psychoses originate in organic cerebral disturbances. The first may be frontal lobe and the latter two diencephalic. The authors do admit, however, to a large constitutional factor in manic depressive psychosis and schizophrenia.

The book would tend to lull students and other readers into a false sense of security. It gives the impression that psychiatry is far more advanced than it actually is.

S.D.

Editorial

The Symposium on Syphilis

THIS issue of the Journal includes a symposium on present day clinical and investigative aspects of syphilitic infection. The guest editors of the symposium have attempted to arrange an integrated and authoritative discussion by men who have made important contributions, with each author assuming full responsibility for his own section. It is hoped that the series as a whole will provide a concise and timely summary of present information. At the same time it must be admitted that some aspects of the subject, notably treatment, are changing so rapidly that there can be no definitive pronouncements at this time, only digests of current information and informed opinion.

There is a widespread impression that the last word, or at least its penultimate expression, has now been reached in the diagnosis and treatment of syphilis. With this we cannot agree. True, the discovery of penicillin by Fleming, its concentration and clinical application by Florey and his associates and its introduction into the treatment of syphilis by Mahoney and his co-workers in 1943 strikingly accelerated progress in the control of this disease. The demonstrated efficacy of penicillin, here discussed by Thomas, Reynolds, Tucker, Solomon and Ingraham, and some of the recent developments in the prolongation of its absorption after intramuscular injection offer hope that we may some day, and perhaps soon, be able to achieve Ehrlich's ideal of a *dosis sterilisans magna*, the total eradication of the invading treponemas by a

single, large dose of a drug which is almost wholly non-toxic to the host. We may confidently anticipate that the incidence of new infections will be reduced to a "manageable minimum." However, that syphilis as an endemic disease can be wholly eradicated is probably only wishful thinking.

The epidemiologic problem, ably discussed by Clark, remains a major obstacle. There remain also wide areas of exploration in the biologic aspects of the disease as indicated by Rosahn. So long as we must rely on a non-specific tissue extract such as antigen for the diagnosis of the disease we will probably be plagued by the problem of non-specific, false positive tests (Neurath). The concentration of one of the reactive principles in that extract (cardiolipin) and the development of confirmatory procedures which may serve to distinguish some of the false positive reactions from those due to actual syphilitic infection will reduce that problem but certainly will not solve it.

The treatment programs thus far evolved are not definitive. Penicillin, by whatever schedule of administration and in whatever dosage it has yet been used, is not effective in every case. In primary and secondary syphilis the proportion of failures has been variously estimated at 5 to 15 per cent and what that proportion of failure will prove to be in the late serious manifestations of the disease remains to be determined. Why these patients with early syphilis are not cured remains as much of a mystery in the case of penicillin as it was with mapharsen

and bismuth. Here certainly is a fruitful area for study.

The possibility of mass immunization with suspensions of pathogenic *Treponema pallidum* is only a hope which may, indeed, prove to be a mirage. That immunity develops in the course of syphilis is incontestable. As indicated in Magnuson's review of that aspect of the disease the dynamics of the development of immunity in syphilis are still being productively explored. However, it does not necessarily follow that the injection of *T. pallidum*, even after the pathogenic organism has been successfully cultivated, will of necessity produce a similar effective immunity. This is nevertheless a possibility which must be exhaustively explored. Here, as in so many other investigative aspects of syphilitic infection, we await the cultivation *in vitro* of a regularly pathogenic *T. pallidum*.

Considerable attention has recently been focused on the prevention of syphilitic infection with penicillin, given by injection or by mouth soon after possible exposure. As an outgrowth of an experimental study on the abortion of syphilitic infection in animals it has been found that a single tablet of penicillin taken by mouth several hours after exposure will effectively prevent gonococcal infection. In syphilitic infection, however, there is unfortunately reason to believe that so simple a procedure will not be effective, due primarily to the comparatively slow rate at which the organisms are killed. The chemical prophylaxis or, more properly, abortion of syphilitic infection by peroral penicillin would probably require so large a dose, or so many repeated smaller doses, as not to be a feasible method for the epidemiologic control of the disease.

Some ten years ago one of us published a

paper with the general title "Current Problems in the Study of Syphilitic Infection," and two years ago a memorandum was drawn up entitled "Outline of Problems in Syphilis Susceptible of Study in the Experimental Laboratory." The fact that most of the points discussed in those two papers are as pertinent today as they were then only serves to underline the difficulty of developing working approaches to these problems and the slowness with which they can be explored. However, that such slow progress has been made does not alter the fact that our greatest single hope for the control and eventual elimination of syphilis as a major public health problem lies in continued intensive exploration in the experimental laboratory of the biology of the infection, its treatment and its possible prevention. The increasing support given to these experimental approaches reflects the general recognition of this fact, and the fortunately close relationship which exists between the experimental laboratory and clinic will permit the rapid and critical trial and exploitation of such advances as will be realized.

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Symposium on Syphilis

Unknowns in the Biology of Syphilitic Infection^{*}

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New Britain, Connecticut

THE twentieth century was inaugurated by a decade which was truly the golden age of discovery in the realm of syphilitic infection. The brilliant investigations of Schaudinn and Hoffmann culminated in the identification of the *Treponema pallidum* as the etiologic agent of syphilis. This was soon followed by Wassermann's classical application of the Bordet-Gengou reaction to syphilitic sera and the development of a diagnostic test based upon the fixation of complement. Only a short time elapsed before Ehrlich announced the epochal discovery that one of several hundred arsenical preparations under study had specific therapeutic efficacy in syphilitic infections. The etiologic agent, a diagnostic laboratory test and a specific therapy of this major human disease were all discovered in a single decade!

Since then in scores of clinics and laboratories throughout the world, investigators have persistently chipped away at the problem endeavoring to disclose the great imponderables of syphilitic infection. In spite of these efforts large segments of the general problem still require precise elucidation. It is the purpose of this communication to discuss those areas in the biology of the disease which merit further exploration.

THE ORGANISM

Over and above all other problems towers one dominating mystery: Why has it not been possible to grow the specific etiologic agent in its pathogenic form on artificial culture media? What are the peculiar and

unknown growth requirements of the pathogenic treponeme which have so far defeated all attempts at cultural propagation? With the possible exception of Noguchi all investigators attempting to solve this problem have met with failure. As a result basic biologic studies have been seriously impeded because of the necessity to employ organisms secured through *in vivo* passage.

Propagation of viruses is possible only in the presence of the living cell. To date propagation of pathogenic treponemes has been possible only in the living organism. Why? What is present in the living host, particularly in man and the rabbit, which is absent in the artificial media thus far employed? Are complex proteins and amino acids the missing links in the chain of growth? Are the requisite factors certain enzymes and hormones and vitamins elaborated by the living host which have not been incorporated in the artificial media heretofore prepared?

Closely related to the problem of the growth requirements of the treponeme is its inadequately understood chemical constitution. Chemical fractionation of the pneumococcus and of the tubercle bacillus has contributed much to our knowledge of the properties of these organisms. Similar studies directed at the chemical constitution of the treponeme should yield significant information. Is there a specific substance in the organism which is responsible for strain specificity and immune reactions? Is there an identifiable chemical component capable of invoking a tissue response similar

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to that produced by the living organism? Would chemical analysis of the organism reveal the presence of lipids and waxes, proteins and polysaccharides and other complex fractions? Systematic studies of the metabolism of the treponeme might provide information directly applicable to attempts at artificial cultivation.

Fundamental studies of the growth requirements and chemical constitution of the treponeme can best be pursued through the cooperative teamwork of specialists in many basic sciences. The bacteriologist and the experimental pathologist, the biophysicist, the biochemist and the physiologist all can make contributions of significance, individually and as a team. In the absence of an available supply of artificially cultivated pathogenic forms would it be possible by *in vivo* methods to obtain a sufficiently large volume of treponemas for chemical fractionation and metabolic investigation? For this purpose could the organisms be separated by centrifugalization from the emulsified tissue containing them? Would this procedure destroy or alter the pathogenic capacities of the resuspended organisms? A large number of animals would be required to provide the reservoir of treponemes for chemical and metabolic studies but the expense and labor involved would surely be minimal in comparison with the potential significance of the results. Not only would such information contribute to our understanding of the antigenic and other characteristics of the treponeme, but reciprocally the whole problem of the cultural requirements of the pathogenic strain might thus be clarified.

The evidence indicating the existence of trophic forms of the treponeme is tenuous when critically examined but studies on immunity suggest quite strongly that strains of treponemes do occur. The work of Chesney and others clearly indicates that a solid immunity can be disrupted by exposure to heterologous strains. Very few attempts have been made to investigate the differential properties of treponeme strains and to classify them on the basis of common

biologic characteristics. It appears not unreasonable to assume that like certain bacteria and viruses treponemes may fall into broad groupings and that one distinguishing property of these groups may be disease-producing capacity. If studies along these lines are successful in demonstrating the existence of classifiable strains of treponemes, many problems pertaining to the human disease may be resolved.

Any discussion of the gaps in our knowledge regarding the biology of the treponeme must give consideration to the controversy over the existence of granular or invisible forms. It will be recalled that Levaditi observed deformed and buckled treponemes at the site of inoculation of the mouse with virulent organisms. Complete disappearance of these forms occurred five days after inoculation. When superinfection of another group of mice was attempted, treponemes could not be demonstrated at the injection site even though control injections of the spleen and other organs from the same mice produced chancres in rabbits. On the basis of this evidence Levaditi concluded that an invisible form of the treponeme was present, accounting for the failure to demonstrate organisms at the site of the second inoculation. Later he observed granular and rolled up forms in infected mouse tissues, particularly lymph nodes, which were virulent as early as twelve to twenty hours following mouse injection even though treponemes could not be demonstrated in them by silver preparations. He concluded that an invisible form of the organism was present in these tissues. Subsequently Levaditi himself, first by using an improved silver stain and later by persistent dark field examination, was successful in demonstrating treponemes in infected mouse tissues. Bessemans and his group likewise noted treponemes on dark field examination of infected mouse tissues and tabulated treponeme counts in a variety of mouse organs. There is no occasion now to doubt that treponemes are actually present in syphilitic mouse tissues although all observers agree that they are extremely few in number. But does their

presence necessarily eliminate the possibility that granular or invisible or transitional forms do occur? This is a problem which to date has not been satisfactorily resolved and indeed may never be settled until the organism has been grown *in vitro*. If these forms do exist, are they similar to viruses, and is this the reason why the treponeme has resisted all attempts at artificial cultivation? Do they, like viruses, require the living cell for their propagation? Can they be demonstrated by differential centrifugalization of emulsified tissue containing active treponemes? Electron microscopy, filtration experiments, dark field motion picture photography at high magnifications and ultraviolet microscopy all have failed to indicate the existence of invisible or transitional forms. The available evidence suggests that such forms do not exist but final conclusions must await the results of critical experiments.

THE HOST

Syphilis, a natural disease of man, can be successfully transferred to a variety of experimental animals. Of these the mouse and the rabbit have been most extensively studied. In each of these three hosts the disease assumes peculiar attributes, many of which have not yet been fully explained. A study of the disease in the mouse, in the rabbit and in man reveals an ascending order of complexity. Each reacts characteristically to the infection yet the disease in each species may at times present manifestations usually associated with one or both of the other two.

Mouse. Syphilis assumes its simplest form in the mouse. Mice inoculated with emulsions of active syphilomas from rabbits have never been observed in reproducible experiments to develop any lesions at the site of inoculation or elsewhere. Nevertheless, tissue from such mice, when transferred back to rabbits, are capable of producing treponeme-containing syphilomas in these animals. Disregarding the possible existence of granular or invisible variants of the organism, several questions immedi-

ately come to mind. What happens to the inoculated treponemes? We know that different tissues of the syphilitic mouse show variable degrees of infectivity for rabbits, but this knowledge throws no light on the fate of the organisms originally inoculated into the mouse. Do they migrate to various tissues and there multiply or once reaching their ultimate destination do they lie dormant? If multiplication does occur, one would assume that tissues from a mouse inoculated, e.g., ninety days previously, would be more infectious for a rabbit and produce lesions following a shorter incubation period in this animal than tissues from mice inoculated with similar material ten days earlier. That this is actually what occurs has not yet been conclusively demonstrated. If it is conceded that treponemes in mouse tissues do multiply, and it is difficult to conceive of a living metabolizing organism at body temperature that does not, then does the rate of their destruction keep pace with their rate of multiplication?

Indirect evidence suggests that destruction of treponemes takes place at a greater rate in the mouse than in the rabbit. Magnuson and Eagle have demonstrated, and their work has since been confirmed, that a rabbit can be successfully infected by the inoculation of a single treponeme. In the mouse, however, the minimal infectious number of treponemes, although not yet established with accuracy, is at least several thousand organisms. What are the peculiar qualities in the mouse economy which prevent organisms below this numerical threshold from obtaining a foothold in the tissues where they may multiply until they reach the level of infectivity for the rabbit? Are the metabolic processes in the mouse different in one or more crucial respects from those of the rabbit? Are unknown treponeme inhibitory factors operative in the mouse and can they be identified and isolated? Such information if it becomes available may be of practical value when applied to the prevention of the disease in man.

The mouse, rabbit and man in this order show an increasing frequency of tissues which react to syphilitic infection. All tissues of the mouse are apparently non-reactive. In the rabbit only the testes, the skin, bone and the eye react with demonstrable lesions. In man no tissue is immune to the development of lesions. Is it possible to define the fundamental biologic differences among these three hosts which are responsible for their differing reactions to syphilitic infection? The mouse is completely resistant to tissue damage even when overwhelming numbers of organisms are inoculated. Can methods and procedures be developed to overcome this tissue resistance and to produce syphilitic lesions in this animal? Certainly such knowledge would be of the greatest import to the understanding of the human disease.

The question may be posed as to whether syphilis in the mouse is biologically a true infection and, further, whether observations on the syphilitic mouse are applicable to an understanding of syphilis in man. Mouse syphilis is apparently analogous to latent syphilis in man, but this analogy is not completely tenable when it is recalled that the syphilitic mouse never develops tissue lesions, in contrast to the human with latent syphilis who occasionally does. The syphilitic mouse appears to be in reality a test tube in which the treponeme is maintained and from which it can be recovered only through rabbit transfer. Is the mouse host in any way disturbed by this symbiotic relationship? So far as is known it is not, although further studies are required before this question can be categorically answered in the negative. What for instance is the influence of syphilis on the longevity of the mouse? The answer to this question must await future study.

Rabbit. The disease in rabbits more nearly approaches the manifestations of human syphilis than it does in the mouse although here, too, significant differences are evident. After inoculation and following an incubation period similar to that observed in man a local lesion develops which

ultimately assumes all of the features of the human chancre. Subsequently, generalized lesions of the bone and skin may occur and occasionally interstitial keratitis and iritis are seen. Clinically and histologically, these lesions are in every way similar to their human counterparts but the course of the disease in rabbits is still fundamentally different from syphilis in man. With the exception of an occasional instance of iritis, secondary lesions do not occur in the rabbit, the skin and bone lesions that are sometimes seen being more like gummas than like secondaries. What factor or factors are operative in rabbit skin that inhibit the skin manifestations which occur in human syphilis? The absence of a maculopapular skin eruption in rabbits may possibly be due to the protective covering of thick fur. This cannot be the entire explanation, however, since the ears of the rabbit have a scant amount of hair and yet a secondary rash does not appear on them.

The original lesion in the rabbit is in every respect similar to the human chancre yet the end results of rabbit syphilis are quite different from those in man. Even though countless numbers of rabbits have been exposed to syphilitic infection, syphilitic lesions of the cardiovascular or central nervous systems have never been observed. Further, gummatous lesions of the visceral organs have likewise never been noted. Here is evidence of organ resistance similar to that which all organs of the mouse apparently possess. Is the absence of syphilitic involvement of the vital organs in the rabbit a real indication of tissue resistance or is some other factor operative? The inoculated organisms must reach the various tissues since they can be recovered from the blood stream early in the infection. Are they destroyed in these organs, particularly in the central nervous system and in the cardiovascular system by some unidentified inhibitory agent? Does the body temperature of the rabbit, which is about 2 degrees above man's temperature, inhibit the growth of the organisms? Or does the true answer to the absence of involvement of vital

organs lie in the relatively short period during which syphilitic rabbits are usually observed? In man symptoms of cardiovascular or central nervous system lesions occur in from five to twenty or more years after infection. Perhaps the incubation period required before disease becomes manifest in these organs is longer than the life span of the rabbit and this is the reason for the absence of visceral lesions. The rabbit lives for about eight years. So far as is known large groups of syphilitic rabbits have never been held for their entire natural life span, with careful autopsies at death to determine the presence or absence of involvement of the nervous and circulatory systems. Such an experiment might throw light on the problem of tissue localization of syphilitic lesions.

In contrast to the as yet unexplained absence of visceral lesions in the rabbit the testes are almost always involved in the syphilitic process, regardless of the mode of inoculation. Warthin has postulated that in man, too, the testes react to syphilitic infection in a high proportion of patients, but recent studies have shown that the anatomic changes in the testes and other organs which Warthin accepted as evidence of syphilis actually occur as frequently in individuals who have never had a specific infection. A satisfactory explanation has never been offered for the frequent localization of syphilitic lesions in rabbit testes. Is it the result of such physical factors as temperature and humidity or is it due to the physiologic fact that rabbit testes are located not only in the scrotum but frequently slip back into the inguinal canal or even into the peritoneal cavity? One other possibility may merit study. The spreading factor described by Duran-Reynals, which is exceptionally potent in testicular tissue, may favor the localization of treponemes in the rabbit testes and their growth therein. If this hypothesis is correct, then the spreading factor in the testes of the rabbit and of man presumably differ, at least quantitatively.

Treponemes localize in the lymph nodes

of the inoculated rabbit. They can in every instance be recovered at any subsequent time by subinoculation of emulsified lymph nodes into a second rabbit, which reacts with an active lesion at the site of inoculation. In this respect the rabbit infection differs from the human disease for rabbit inoculation of excised lymph nodes from syphilitic patients only occasionally results in the production of a lesion in the inoculated animal and then only in the early phases of the human infection. Why are treponemes generally not demonstrable in the lymph nodes of latent human syphilitics while in rabbits they can always be recovered from lymphoid tissue? Is this not an indication of a fundamental biologic difference between the two species, and does not this difference suggest that information based upon rabbit investigations be applied to man only with the greatest of caution?

An extension of this thought suggests still another difference between the rabbit and the human disease. There is good evidence now that asymptomatic infection of the rabbit does not occur. Careful and frequent examination of the inoculation site invariably reveals the presence of a lesion in which treponemes can be demonstrated. When such examinations fail to disclose a lesion, the draining lymph nodes do not produce chancres in subinoculated rabbits. In man, however, many reliable and cooperative witnesses when discovered to be infected fail to recall any primary or secondary lesions. This testimony is so frequent that the occurrence of asymptomatic infection in man must be accepted. Here again is a distinguishing feature between the rabbit and the human disease which requires explanation.

Man. The study of syphilitic infection in the laboratory animal presents no real difficulties since experimental procedures in this instance are limited only by the particular interest, ingenuity and technical skill of the investigator. Experimental techniques are not so readily applicable to study of the human disease in which reliance

must be placed largely on historical data, case histories, statistical assays and laboratory and autopsy findings. Augmenting these approaches, insight into the human disease can sometimes be obtained by analogy with animal observations, but objective evidence in support of such conclusions is frequently difficult to secure. There are innumerable unsolved laboratory and clinical problems in human syphilis; every student of the disease can recall many problems with which he is repeatedly confronted in his own field of special interest. Here an attempt will be made to discuss general problems having broad clinical implications. Much work and clear thinking will be required before they are finally solved.

First there is infection, and infection is acquired predominantly through contact of mucous surfaces. An infected source has contact with two individuals within close time intervals. The first develops syphilis, the second does not. What is the explanation for this occasional difference in response? Does it depend on the total number of available organisms at the source of infection? In rabbits inoculation of a single organism is frequently sufficient to infect; in the mouse several thousands are required. What is the minimal number of treponemes necessary to establish infection in man? Does the number of organisms vary in the same open infecting lesion and, if so, what are the factors influencing this variability? If the treponemes in a fresh lesion are numerically constant, does the susceptibility of individuals coming in contact with this lesion vary? And if this variability exists, is the number of organisms required to establish an infection in one individual insufficient to initiate infection in another? If strains of treponemes exist, does the minimal infectious number vary with the strain or is natural immunity strain-specific rather than species-specific, and is this the reason why one individual fails to develop syphilis following contact with an infected source while another after contact with the same source does become infected?

We know very little about natural or specific immunity to syphilis in man. However, certain conclusions have withstood the test of time and are now generally accepted. Well controlled surveys have repeatedly demonstrated that syphilis is less frequent in the female than in the male and this is independent of race. Moreover, in a group of known syphilitics the disastrous late complications of the disease, i.e., cardiovascular or central nervous system involvement, are likewise less frequent in the female than in the male. A possible explanation for this difference lies in the differing hormonal production of the two sexes, a conclusion which gains credence by the general impression that pregnancy may exert a benign influence on the lesions of early syphilis. Here we have an observation and a tentative conclusion, but little has been done to determine the specific hormones that may be involved in the suppression of syphilitic manifestations in the female or in the enhancement of these manifestations in the male nor do we know the mechanism by which these results are produced. This is clearly a field which merits further investigation.

In the rabbit natural immunity to syphilis is demonstrably a function of breed; in man it has been observed that race influences the reaction to syphilis but how breed in the rabbit or race in man accomplishes this effect is not known. It is customary in a consideration of racial differences to rely upon physical constitution and skin pigmentation as distinguishing determinants, but biologic differences are also present as can be demonstrated in the rabbit. The hemocytologic pattern of rabbits differs significantly among different breeds, and indeed this pattern has been successfully used as an index to prognosticate the outcome of subsequent inoculation with a transplantable tumor. How the hemocytologic formula of rabbits exerts this influence is not known, but a high degree of correlation does exist between pre-inoculation blood cell levels and the response to the Brown-Pearce tumor. In

man, too, the hematologic formula differs significantly among individuals, and it is entirely possible that natural immunity to a chronic disease like syphilis may be related, at least in part, to the individual blood cell formula. Other biologic factors of a non-specific type may also be involved in individual or racial susceptibility to syphilis, factors such as the blood levels of various organic and inorganic compounds, the pH of the blood and tissues, the carbon dioxide combining power of the blood or other biologic variables which can be quantitatively evaluated.

Once infection has been established, a complicated series of events aimed at suppressing it takes place within the host. Comparatively little is known about specific immunity in syphilitic infection in man. The usual antigen-antibody reaction is not operative. Antibodies capable of neutralizing the infectiousness of treponemes are not produced, nor is it possible to demonstrate agglutinins or precipitins which are effective against the living organism. Nevertheless, there is good evidence that a real immunity develops in syphilitic infection. Many persons known to have been infected live their lives through without serious inconvenience and, indeed, lesions of syphilis recognizable as such during life or at autopsy may never develop in them. What are the factors which cause the suppression of tissue changes in these instances? Only a small percentage of infected persons ever develops specific lesions in the central nervous or cardiovascular systems. What influences are operative to localize the infection in these vital organs in some persons, or to inhibit the development of specific lesions in others? Are they of a physiologic nature, blood flow for instance? Are they related to variations in the tissue metabolism of the infected host or are they characteristic of a true immunity the exact nature of which is still unknown?

The *modus operandi* of serodiagnostic tests for syphilis requires further study. None of these procedures employs a specific antigen yet it is apparent that a positive serologic

test for syphilis is quite definitely related to syphilitic infection for serologic positivity is significantly more frequently associated with anatomic lesions of syphilis than is serologic negativity. In spite of this how can we explain the fact that about one-fourth of syphilitics in whom lesions of syphilis are found at autopsy were serologically negative during life, or the fact that many diseases other than syphilis frequently exhibit positive serologic reactions, or the fact that normal uninfected and presumably healthy persons are encountered on occasion with sera which give positive serologic tests? The work of Neurath holds great promise of resolving the dilemma, but the true nature of the antibody response in syphilis requires further study before the mechanism of serologic tests is clarified.

There is much talk of reagin, but the exact nature and characteristics of reagin have yet to be defined. Positive serologic tests for syphilis have been induced in the rabbit by repeated injections of killed treponemes which suggests that reagin is a specific antibody to the organism. If this is true, one would expect that the presence of reagin would offer protection against infection, but this inference is not substantiated by the observation that rabbits with induced positive serologic tests for syphilis were not protected against infection. Traditional concepts of antigen-antibody interaction fail to explain either the serologic reactions employed as a diagnostic test for syphilis or the immunity known to be established in the course of the infection. New and perhaps unorthodox working hypotheses will be required before the apparent paradox is understood. In the last analysis it is likely that complete understanding will have to await the successful artificial cultivation of the pathogenic agent.

Almost a decade has elapsed since Moore emphasized our lack of knowledge of the time and method of fetal infection in congenital syphilis. Little has been done since then to add to our understanding of this problem. Congenital syphilis has never been

observed in the experimental animal. In the mouse ovarian tissue and blood have been shown to be infectious for rabbits although the offspring of mothers on whom these tests were carried out were not themselves infected. Studies on the syphilitic rabbit have demonstrated the infectious agent in blood, uterus and placental tissue. In spite of these findings the offspring of similarly infected rabbits observed in parallel regularly failed to demonstrate any indication of congenital syphilis. Congenital syphilitic infection is apparently unique in the human species. The simplest explanation—that infection of the fetus occurs through passage of treponemes via the placenta from the maternal blood stream—implies a sequence of events which is difficult to accept. It suggests that a syphilitic woman, whose infection may be of several years duration and who may reveal no clinical manifestations of the disease, develops a blood stream infection at the time of or soon after impregnation. This invasion of the maternal blood stream by treponemes moreover is not accompanied by any clinical indication of tissue lesions. The infectious agent then passes through the placental barrier to the fetus in which evidence of infection is delayed until approximately the fifth month of gestation or later. This hypothesis calls for an explanation of many aspects of the problem, among which are the following: (1) How does the state of pregnancy incite a blood stream invasion in a woman whose disease is of several years' duration? (2) How can we account for the fact that in the presence of this hypothetical treponemia the pregnant syphilitic woman does not develop syphilitic involvement of her tissues? (3) How can we explain the delay in the tissue manifestations of syphilis in the fetus until about the fifth month of gestation? These questions have been asked before but the answers to them are not yet at hand. Perhaps the entire explanation lies in a simpler working hypothesis, here offered as a basis for further investigation.

At the time of infection (according to this hypothesis) treponemes are distributed

throughout the host, lodging in various organs, including the uterus. They soon reach a state of equilibrium but retain their potential capacity for proliferation and invasion. After impregnation the uterus, no longer static, actively expands to accommodate the developing fetus. Concomitant with these uterine changes the treponemes located in the uterus participate in the activity by multiplying and invading, ultimately lodging in the amniotic fluid. Fetal infection takes place through this fluid which reaches the pulmonary tissue as a result of the intrauterine respiratory movements of the fetus. These movements, noted as early as the twelfth week of gestation, continue in the fetus throughout intrauterine life. If infection of the fetus actually takes place in this manner, it will account for the fact that signs of congenital syphilis are rarely if ever observed earlier than the fifth month of fetal existence. The time of onset of intrauterine respirations, added to the time elapsing before infection actually occurs, plus the incubation period for the production of lesions, totals approximately five months. Continuous contact with infected amniotic fluid may perhaps explain the pathogenesis of pneumonia alba. Following pulmonary infection, generalized dissemination of the organisms occurs via the blood stream. The first step in verification of this hypothesis will necessarily be to determine whether the amniotic fluid of the syphilitic mother is infectious early in pregnancy. Aspiration of amniotic fluid apparently carries no risk to the mother and can be performed in selected cases by needle puncture through the abdominal wall and uterus. The hypothesis presented here may not explain all of the factors in the pathogenesis of congenital syphilis but it suggests an approach to the problem which warrants investigation.

Arsenotherapy for syphilitic infection was introduced in 1910. Now, in 1948, we still lack precise knowledge of the effectiveness of this form of treatment in preventing the late disastrous manifestations of the disease. Carefully controlled clinical studies checked

by routine autopsy surveys and based upon statistically adequate samples have yet to be pursued. The work of Bruusgaard on the end results of untreated syphilis is well known and this has been confirmed by a recent review of autopsy material. But no similar report has appeared on the end results of adequately treated syphilis on which to base a comparison and by which it can be determined with a fair degree of accuracy just exactly what arsenotherapy did accomplish. It is to be hoped that this will not be said about penicillin thirty years hence.

Penicillin has revolutionized the therapy of syphilis. It has reduced the hazards associated with heavy metal treatment systems, it has shortened the duration of treatment, it has increased the number of patients who complete the prescribed treatment regimen, it has been outstanding in its prevention of prenatal syphilis and in its beneficial influence on infantile congenital syphilis, it has been highly effective in early acquired syphilis, in the benign gummatous lesions of late syphilis and in neurosyphilis. Organized cooperative clinical studies have within a relatively short time been eminently successful in defining the usefulness and limitations of the drug. But equally important, the introduction of penicillin has stimulated investigations on the biology of syphilitic infection which promise to be as significant as the therapeutic effectiveness of the drug itself. A fundamental study, for example, is the determination of the mode of action of the drug. Recent work in this direction suggests that penicillin causes a disturbance in the uptake of amino acids by susceptible organisms. It is conceivable that an extension of these studies may contribute to our knowledge of the metabolic functions of the treponeme and that this information in turn may well lead to the successful artificial cultivation of the pathogenic form. Similarly, the evaluation of penicillin in early syphilis has directed attention to the important distinction between relapse and reinfection and to the

biologic factors responsible for these clinical entities.

Through studies on the therapeutic efficacy of penicillin in syphilis our knowledge of the disease has been expanded and attention has been directed to numerous problems which call for solution. Joseph E. Moore has recently presented a provocative discussion of many of these problems among which he lists the following:

"Why is early syphilis uniformly curable in the rabbit with proper adjustment of time and dose, whereas in man, no matter what the treatment system employed, there is a substantial residue of failure?"

"Why are not the synergism of penicillin with arsenic, the additive effect of bismuth, or the enhanced effect of penicillin given at fever temperatures equally demonstrable in man and rabbit?"

"What is the significance of low titer seroresistance in early syphilis after penicillin (or any other) treatment, i.e., the persistence of a small quantity of reagin in the blood over a long period of time?"

"Can any criteria be devised which will serve to differentiate reinfection from relapse?"

"What is the effect of penicillin on resting versus rapidly dividing *T. pallidum*?"

"What is the relationship of the time-dose factor of penicillin treatment to the rate of multiplication of *T. pallidum*?"

"Does prolonged seronegativity in man after the penicillin treatment of early syphilis indicate cure?"

"Why should fetal infection, which is often massive and overwhelming as compared to the acquired disease in adults, be so readily and completely curable as the result of a fetal tissue concentration of penicillin substantially lower than that in the maternal body?"

"Is late syphilis in man also curable with this drug?"

"Are the good results in neurosyphilis permanent?"

It is penetrating questions such as these which will serve as a stimulus to investigators of the future.

And what of the future? How best can our resources be organized and coordinated in a frontal attack on the problems just outlined and on others that come readily to mind? Available funds in the past have been largely utilized for clinical and epidemiologic studies. These have served and are serving their useful purposes; they have advanced our understanding of diagnostic and therapeutic problems in syphilis, they have been responsible for reducing the public health hazards of the disease and they have contributed in large measure to fundamental concepts in the biology of

syphilitic infection. It is apparent, however, that many of the basic problems in syphilis can be solved only through laboratory research. To this end encouragement should be given not only to the serologist, the bacteriologist and the pathologist but also to investigators in the basic sciences of physics and chemistry. Modern techniques in physical and chemical research, not excluding those of atomic exploration, can well be adapted to elucidating many of the mysteries in the life history of syphilitic infection. In this direction lies greater knowledge and understanding.

Current Concepts of Immunity in Syphilis*

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THE advent of rapid treatment methods for syphilis has renewed interest in the problems of immunity in this disease. Such renewal arises with each therapeutic advance since a more adequate knowledge of immunity is required for the proper evaluation of therapeutic results. It is also essential for the interpretation of the fundamental biology of the infection as it relates to latency, clinical progression, relapse and their attendant problems. An understanding of the mechanisms involved may eventually render possible the production of this immunity by artificial means although the end is not now in sight.

The purpose of the present review is to summarize current knowledge of immunity in syphilis and to examine in some detail the pertinent experimental and clinical literature appearing since Chesney's monumental review¹ in 1927. For a discussion of the older literature the reader is referred to Chesney,¹ Neisser,² Levaditi³ and Bruck.⁴ More recent summaries have been those of Urbach and Beerman,⁵ Worms⁶ and Truffi.⁷

Unfortunately, the term "immunity" has been employed differently by various authors. By some the term has been confined to an almost solid resistance against infection while others have included any alteration in the host's response to infection. As used in the present review "immunity" may better be interpreted as "resistance." Discussion will be limited to those factors modifying the host's resistance to infection by *Treponema pallidum*. In evaluating these factors, the relationships between the infecting organism and the host are most complex, and neither the factors involving

the host nor the infecting organism can be considered independently, nor can they be considered in a mere qualitative sense. A quantitative approach is requisite to an understanding of the multiple factors involved.

NATURAL IMMUNITY

Natural immunity or resistance includes those factors not due to previous experience with the infecting organism which modify the host's susceptibility to infection. Such resistance may be local or general but in many instances the degree to which each contributes cannot be ascertained.

There has been no evidence to refute the belief that syphilis is a disease occurring naturally in man alone. A symptomatic disease has been produced in apes and in rabbits which runs a course analogous to if not identical with that in man. Both species have been used experimentally although nearly all of the recent experimental work has been done in the rabbit. Since the appearance of Chesney's review,^{8,9,10} ample evidence has been brought forward that many animals, e.g., mice, rats, guinea pigs, hedge-hogs and hamsters, previously thought immune to syphilis, may be infected experimentally, but that in such animals the disease remains asymptomatic. The infection may be demonstrated in these animals by transfer to a susceptible host or in some instances by staining of the *Treponema* by suitable silver stains. There is at the moment no adequate explanation for the asymptomatic course of the infection in these animals. It is known that the organisms may survive for long periods of time and multiply in the asymptotically

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infected host. The tissues do not respond with clinically or pathologically demonstrable lesions; and so far as is now known, the infection is without deleterious effect upon the animal. Since the results of infection in these species are the same regardless of the route of inoculation, it would appear that whatever the mechanism of this resistance it is a systemic phenomenon.

In rabbits there are some differences in natural resistance to infection as measured by the number of spirochetes required to produce the disease. Morgan and his co-workers^{11, 12, 13} observed that a single *T. pallidum* failed to produce infection, larger numbers produced asymptomatic infection and the intratesticular inoculation of some twenty to one hundred organisms usually produced symptomatic infection. Bessemans¹⁴ noted that approximately 10 per cent of the rabbits failed to develop symptomatic infection when given the usual inoculum but such animals were actually asymptotically infected. No quantitative data are available as to the size of the inoculums.

These findings differ from those reported by Magnuson, Eagle and Fleischman¹⁵ who found that the minimal infectious inoculum of the Nichols strain of *T. pallidum* on intratesticular inoculation was one spirochete. The infectious inoculum by the intracutaneous route was somewhat higher, approximately five spirochetes producing infection in 50 per cent of the animals. Under their experimental conditions these same authors found asymptomatic infection extremely rare in normal animals. Failure to develop symptomatic disease nearly always meant that the animal had escaped infection. Similar findings have been recorded by Rake¹⁶ who, in his use of the abortive treatment of syphilis for therapeutic assay of penicillin, found a similar negligible incidence of asymptomatic infection. The discrepancies in the incidence of asymptomatic infection in normal animals reported by Magnuson and his co-workers and Rake and his co-workers, as contrasted with the older findings of Morgan and of Bessemans,

may perhaps be attributed to differences in the adaptation of the strains used and in the rigidity with which environmental factors were controlled. It is now well recognized that for rabbits to develop symptomatic infection regularly it is necessary to keep them at an environmental temperature below 75°F. Magnuson, Eagle and Fleischman¹⁵ have described additional factors related to the parasite which they believe may be partially responsible for discrepant results. The degree to which a similar low incidence of asymptomatic infection applies to man is unknown since small lesions may be overlooked by the patient resulting in an asymptomatic infection in practice if not in fact.

In the experiments cited, organisms were inoculated directly through the natural barriers imposed by skin or mucous membrane. Probably such barriers are important in the resistance of animals and man to infection but it is difficult to evaluate the relative importance of these barriers. Mahoney and Bryant¹⁷ have shown that the rabbit may be infected by exposing the unbroken mucous membrane of the prepuce to spirochetal emulsion and that such infection presumably takes place through the intact mucous membrane. It is interesting to note the report of Wilson¹⁸ who found the incidence of primary syphilis among soldiers in the Canadian army during the past war significantly higher in uncircumcised than in circumcised males. Presumably factors influencing local resistance were responsible.

A brief study by Frazier²¹ suggests that the manifestations of the experimental disease may differ in certain strains of rabbits. When seven albino and eight brown rabbits were inoculated with Nichols strain of *T. pallidum*, the former developed a more intense orchitis of longer duration than the latter animals. This same group showed a higher incidence of a metastatic keratitis with six of the seven albino animals developing metastatic eye lesions while only one out of eight brown rabbits developed such lesions.

Rosahn²² compared the severity of experimental syphilis in five standard breeds of rabbits by measuring the frequency, time of occurrence and severity of various metastatic lesions. The English, Himalayan, and Rex rabbits were considered more susceptible than the Havana and Dutch breeds.

There is no indication of a true racial immunity to syphilis in man although evidence suggests that the course of the disease and the nature of clinical manifestations may show some variation. Perla¹⁹ believes that such apparent variations in natural racial resistance are due to differences in the opportunities for infection as determined by previous saturation of the population with the disease. Interesting speculation as to the rôle played by racial and environmental factors in such as resistance has been advanced by Hudson.²⁰ He believes that yaws and syphilis are identical diseases caused by the same organism and that the clinical differences may be attributed to long-standing environmental factors.

In the absence of inoculation experiments it is impossible to assess accurately the degree to which natural immunity may occur in man. Recent studies²³ have indicated that approximately 50 per cent of the named contacts of primary and secondary syphilis apparently escaped infection. Interpretation of such findings is difficult since the degree of contact between the infectious patient and his contact is unknown. If effective contact occurred, there is no information as to the size of the inoculum, site of inoculation or whether infection failed because of local factors preventing penetration or by reason of systemic factors which overcame the invading organisms. Determination of the degree of natural immunity in man must be deferred until these inoculation variables can be controlled.

ACQUIRED IMMUNITY

Acquired immunity comprises that resistance of the host to infection which is dependent upon the host's previous experience with the same or related infecting

organism. While it is recognized that much of the animal data on acquired immunity are not directly transferable to man, the multiple variables preclude answering many questions by clinical means alone. The known clinical facts are paralleled to a remarkable degree by the findings in experimental animals, and this correlation suggests that new experimental findings may have their counterpart in the human infection. Many of our basic concepts of acquired immunity have had to rest upon such animal evidence.

Factors involving the infecting organisms which appear to influence the course of acquired immunity include: strain of the organism, virulence of the organism (for the particular host) and size of the inoculum. Host factors include: duration of the original immunizing infection, site and manner of the first and second inoculations and possibly the degree of systemic or local reaction to the original infection. The interaction of these factors may be expressed as a complete immunity, a partial immunity, no immunity or perhaps an increased sensitivity to the organism or its products. The degree to which these various factors influence the interpretation of our present knowledge of immunity in syphilis will be indicated below.

At the time of Chesney's monograph experimentalists were divided into two schools regarding the existence of acquired immunity. This difference of opinion is still unresolved although the weight of present evidence would seem to support the view of Chesney. Generally speaking, the author's experiments indicated that a true acquired immunity developed during the course of experimental syphilis. In summarizing his own and earlier experiments he demonstrated that the determining factor in the development of such immunity was the duration of the primary or immunizing infection prior to its termination by treatment. If the immunizing infection lasted less than three months, reinoculation of the homologous strain by the same route as the original inoculation was usually

followed by clinical reinfection. If the immunizing infection was terminated by treatment after three months, similar reinoculation with the homologous strain usually did not result in symptomatic reinfection. The experimentalists agree on these observations, but differ as to whether this failure to react to the second infection represents a true immunity, or whether it represents an altered reactivity of the animal due to the persistence of the original infection. Chesney's experiments and those of Uhlenhuth and Grossman,²⁴ Vasarhelyi,²⁵ Gastinel²⁶ and Worms,⁶ among others, have shown that animals could be cured with various arsphenamine drugs as shown by node transfer, and that these cured animals remained immune to subsequent reinoculation. This view is contested by Neisser,² Finger and Landsteiner,²⁷ Kolle and Prigge,²⁸ and Truffi⁷ who maintain that failure to reinfect an animal is due to the persistence of the original infection and, that if the original infection is cured, no true immunity remains.

The position taken by Kolle and Prigge is well summarized in their experiments reported in 1934.²⁸ Rabbits were inoculated with either the Nichols or Truffi strains of *T. pallidum* and treated 319 to 328 days later with doses of salvarsan ranging between 0.01 Gm. to 0.3 Gm. per Kg. of body weight. Node transfers one year after treatment were negative on the animals given the highest (0.3 Gm.) dose. One of fifteen animals given the middle dose (0.03 Gm./Kg.) was positive and eleven of eighteen animals given the smallest dose (0.01 Gm./Kg.) were positive. The animals were then reinoculated with the homologous strain of *T. pallidum*. None of these animals developed a chancre. Two hundred eighty-one to 296 days after reinfection the node transfers were repeated. Of animals receiving the highest dose of neoarsphenamine, seven of twenty were positive on node transfer; with the intermediate dose, one of seven was positive; and with the small dose, one of five was positive. Kolle and Prigge concluded that these animals had a

so-called chancre immunity but denied the existence of true acquired immunity; of twenty animals treated with the largest dose seven developed asymptomatic reinfection. Since animals treated with smaller amounts of neoarsphenamine were not regularly cured, the incidence of asymptomatic reinfection could not be evaluated in these animals. The authors suggested that the apparent discrepancy between their results and Chesney's might be attributable to the fact that Chesney gave his challenging inoculations shortly after the arsenical therapy, possibly permitting the slowly excreted arsenic to serve as a prophylactic against the second inoculation.

It is the present reviewer's opinion that the results of these experiments do not bear out Kolle's conclusions. Although the animals had been cured as demonstrated by the negative node transfers, the animals were resistant to symptomatic reinfection. Thus, "chancre immunity" was not dependent upon the persistence of the original infection. Of the twenty animals carried to the end of the experiment, thirteen were completely resistant to the inoculum used as confirmed by negative node transfers. The fact that seven of the twenty animals developed an asymptomatic reinfection probably indicates partial immunity in these animals. The quantitative relationships between these types of results will be discussed below. The suggested prophylactic action of previous therapeutic neoarsphenamine has been excluded by other authors.²⁶

More recently Vaisman³⁰ concluded on the basis of two superinfection experiments in rabbits that syphilis did not confer true immunity at the various stages of its evolution. In the first experiment six rabbits were inoculated intravenously with *T. pallidum* (Truffi strain), were untreated and then reinoculated subscrotally with the same strain seventy-three days after the first inoculation. Of the six animals two developed no chancre and four developed unilateral or bilateral syphiloma. These same animals were reinoculated again 152 and 205 days after the preceding tests.

Only one of the six rabbits developed a typical chancre. The author concluded that six months after the first infection chancre immunity was not always constant. In a second experiment twenty-six animals were infected with one of three different strains (Truffi, Gand, Gim) and were reinoculated from the forty-third to the two-hundred twenty-eighth day with a heterologous strain. Thirteen (50 per cent) of the animals developed chancres. The authors noted that on reinoculation the incubation period was shorter and the chancres tended to be more necrotic and in some cases tended to reach a much larger size. These experiments would indicate that chancre immunity is not always complete even by the sixth month, especially when the challenge is made by the heterologous strain. The experiments do not contribute to the solution of the fundamental problem outlined above.

The older data suggesting that immunity is dependent upon persistence of the original infection have been adequately reviewed by Chesney.¹ In general, his analysis of the older work indicated that the critical factor, previously overlooked, was the duration of the primary or immunizing infection prior to its termination by treatment.

Numerous studies appearing since Chesney's review substantiated his conclusions. Grossman³¹ treated twenty-seven syphilitic rabbits with large doses of salvarsan at 118 days to several years after the first infection. Twenty-nine days after treatment they were reinoculated either intratesticularly or intravenously. Only one animal showed manifest local symptoms and the rest remained clinically negative. In five of the twenty-three clinically negative animals spirochetes could be demonstrated by transfer of lymph nodes and organs. The others were negative. The author concluded that rabbits could be absolutely immunized against syphilis. As the author pointed out, the fact that spirochetes were found in five animals does not disprove this since failure of treatment or individual failures in the development of

immunity might account for these exceptions. Among six rabbits treated in the late stage with large doses of salvarsan and reinoculated by the intratesticular route five and one-half to seventeen months later, one animal showed indeterminate local changes and the others remained negative. In these five animals the virus could be demonstrated by transfer of glands and organs. The author concluded that the absolute protection was of relatively short duration.

Somewhat similar results were encountered by Gastinel, Pulvenis and Collart.²⁹ Rabbits given scrotal inoculations with the Hoffman strain of *T. pallidum* were treated 100 to 120 days after inoculation with 100 mg./Kg. of neoarsphenamine weekly for seven weeks. Challenging infection was given one and one-half to twenty months after the last treatment. Confirming the efficacy of treatment, node transfers performed just before challenging inoculation were negative. The reinoculated animals were observed for six weeks and if they remained clinically negative a second node transfer was done to determine whether or not latent infection had occurred. Of twenty-four animals reinoculated within ten months from the end of treatment there was one abortive syphiloma which occurred in an animal reinoculated two and one-half months after treatment. One rabbit inoculated after three months and another after six and one-half months developed a latent form of syphilis as shown by positive lymph node transfer. The other animals developed neither symptomatic nor asymptomatic infection. Of nine animals reinoculated ten to twenty months after treatment three developed typical syphilomas. The others were free of inapparent or latent infection. In one rabbit the reinoculation was negative at fourteen months; but when reinoculation was repeated at twenty months, a typical syphiloma developed. Recognizing Kolle's²⁸ objection to a short interval between the administration of drug and reinoculation, the authors treated seven control rabbits with the same amounts of neo-

arsphenaminic. With but one exception all of these animals could be reinfected after an interval of twenty-five to thirty-five days from the last injection indicating that retention of drug was not responsible for failure of reinfection in the experimental group. The authors concluded that within ten months from the end of treatment positive reinoculations (unapparent or latent) were observed in 12.5 per cent of the cases, syphiloma in 4.1 per cent, latent infection in 8.4 per cent. In the first six months the only lesion observed was the abortive type of chancre. From ten to twenty months after treatment reinoculation was followed by the development of typical syphilomas in one-third of the animals tested. These data suggest that the immunity decreased with the passage of time.

Vasarhelyi²⁵ treated sixteen rabbits after 110, 247, 333 and 409 days with large doses of salvarsan (three doses of 0.10 Gm. each per Kg. of body weight). Challenge was made from eighty to ninety days after treatment. None of the animals developed clinical reinfection. All of the control animals infected at this same time developed syphilis. Node transfers on animals failing to develop lesions were performed 75 to 127 days after reinoculation. Only four of these node transfers were positive.

Recent experiments of Arnold, Mahoney and Cutler^{32,33} have shown a similar immunity in rabbits following penicillin therapy. Thirty-seven rabbits were treated with curative amounts of sodium penicillin six to eight weeks after inoculation. Ten days after therapy challenge was made with the homologous (Nichols) strain by the same subscrotal route. Ten of the animals (27 per cent) developed symptomatic reinfection with darkfield positive chancres at the site of reinoculation. The remaining twenty-seven rabbits (73 per cent) developed asymptomatic reinfection as demonstrated by the absence of clinical lesions during a fourth-month observation period and positive node transfers at the end of this time. In a similar experiment in which treatment was given to thirty-four

rabbits eight months after inoculation, the same challenge inoculation produced no symptomatic reinfections, asymptomatic reinfection in eighteen (53 per cent) and no infection in sixteen (47 per cent). Thus, a significant percentage of the animals were completely immune to the challenging inoculum employed.

Gastinel, Collart and Mollinco³⁴ reported that rabbits treated with penicillin six months after inoculation were completely resistant to reinoculation.

Magnuson and Roscnau³⁵ have attempted a more precise quantitative measurement of the rate of development and the degree of acquired immunity in experimental syphilis. Since the infectious inoculum for normal animals with the Nichols strain of *T. pallidum* is extraordinarily small,¹⁵ it was believed that degree of immunity might exist which could be demonstrated only by using small challenging inoculums. In nearly all previous experiments the challenging inoculums were far in excess of the minimal infectious inoculum so that an extraordinary degree of resistance was required to demonstrate any immunity. In Magnuson's experiments rabbits were inoculated either intratesticularly or intracutaneously with the Nichols strain of *T. pallidum* and treated with either mapharsen or penicillin three, six, twelve or twenty-four weeks after inoculation. Six weeks after treatment the animals were challenged by carefully graded inoculums of the homologous strain of *T. pallidum*. Such reinoculations resulted in either symptomatic reinfection (darkfield positive lesion at site of reinoculation), asymptomatic reinfection (no lesion at site of inoculation but node transfer positive) or immunity (no lesions and node transfer negative). Using this quantitative technic, immunity was demonstrated as early as three weeks after inoculation and was progressive in degree throughout the twenty-four-week period studied. This increase was determined by the progressive increment in the number of organisms required to produce a given response on reinoculation. At the twelfth

week more than ten million minimal infectious inoculums were required to produce symptomatic reinfections, and by the twenty-fourth week 50 per cent of the animals were completely protected against 200,000 minimal infectious inoculums.

The quantitative data suggest that asymptomatic reinfection represents a partial immunity sufficient to destroy the majority of the spirochetes so that no local lesion develops but insufficient to destroy all of the spirochetes. Some spirochetes reach the regional lymph nodes. This phenomenon of asymptomatic reinfection was probably first recognized in immune animals by Chesney and Kemp³⁶ who believed that such an occurrence in humans might be responsible for a considerable number of the so-called serologic relapses assumed to be treatment failures. In their experience all of the animals developing asymptomatic reinfection developed an apparent serologic relapse. This finding has been partially confirmed by Magnuson.³⁷ Animals developing asymptomatic reinfection after a short primary immunizing infection have developed an apparent serologic relapse, but asymptomatic reinfection developing in animals with a twelve- or twenty-four-week immunizing infection have not been accompanied by such relapse.

The degree to which such quantitative findings may be applied to infection with heterologous strains of *T. pallidum* is as yet unknown. All of the older experimental work (cf. Worms⁶) would indicate that a partial immunity develops to heterologous strains but that it is of much smaller degree than that developed against the homologous strain. Worms⁶ attempted demonstration of a pan-immunity by producing the immunizing infection with a mixture of three old strains of *T. pallidum*. Subsequent challenge with a fourth strain did not result in infection indicating that in this instance the immunity was not strain specific.

Variation in the site and manner of the first and second inoculations may alter the apparent degree of immunity, which sug-

gests the presence of local factors increasing resistance.¹ It is possible that preceding lesions may have occluded lymphatic channels preventing systemic spread of the organisms.³⁸ Chesney, Woods and Campbell³⁹ showed that animals with a systemic immunity demonstrable by usual inoculation technique could often be successfully re-inoculated by injecting the challenging organisms either into the cornea or the anterior chamber. The suggested explanation is that the poor blood supply of the cornea either does not provide the corneal cells adequate antigenic stimulus at the time of the original infection, or that the same circulatory inadequacy may prevent penetration of some systemic antibody which would prevent infection.

Chesney and Woods⁴⁰ later reported on the development of immunity following original intracorneal inoculation. Such inoculation was followed by systemic spread of the disease and the development of a systemic immunity more marked on intracutaneous challenge than on intracorneal challenge.

CROSS IMMUNITY

There is some clinical evidence that infection with either yaws or syphilis may protect against the other of the two diseases. While a few human inoculation experiments have indicated that yaws may not confer an appreciable degree of immunity against syphilis, Turner⁴¹ suggested that these apparent failures might be due to the fact that the re-inoculations were performed too early in the course of the yaws infection. A careful clinical study showed that resistance to superinfection developed slowly in clinical yaws. Resistance to autogenous inoculation occurred early in the disease developing during the period of active lesions. Resistance to inoculation with heterologous strains of yaws spirochetes evolved much more slowly. During the first three years of the infection re-inoculation with a heterologous strain was followed by a modified or abortive type of yaws. After a period of ten years the majority of yaws

patients were refractory to such reinoculation. Thus attempts to measure the immunity of yaws patients to syphilis during the course of the active yaws lesions are doomed to failure. Such attempts at cross inoculation should be performed after the patient had had his yaws for some years.

Cross inoculation experiments between yaws and syphilis in experimental animals have been studied by a number of authors. The results are not in entire agreement. Kato⁴² inoculated rabbits either subserotally or intratesticularly with frambesia. The rabbits were then superinfected three times in succession, the first and second times into the skin of the back and the third time into the scrotum. Thirty-one days after the fourth infection or the third superinfection *T. pallidum* were inoculated into the back at eight spots in different quantities. The emulsion was serially diluted 1, 20, 30, 90, 180, 360, 720 and 1,440 times. These inoculations all became positive and did not differ greatly from those produced in normal controls although the incubation period was somewhat prolonged. Kato believed that no cross immunity had been demonstrated.

Maisaizu⁴³ inoculated rabbits intracutaneously with yaws and treated with salvarsan at periods varying from twenty to seventy days after inoculation. The immunity was challenged by the subsequent intravenous inoculation of *T. pallidum*. The only difference noted in the course of the yaws animals and the control animals was that the incubation period was a little longer in the former group.

Turner, McLeod and Updyke,⁴⁴ using the delay in incubation period as a measure of resistance, were able to demonstrate that within six months after intratesticular inoculation of *T. pallidum* or *T. pertenue* or *T. cuniculi* an appreciable degree of immunity developed which was effective in protecting the animals against intracutaneous challenge with the heterologous spirochete. They also noted that the immunity produced by infection with *T. cuniculi* seemed to be somewhat lower in degree than the resistance produced by *T. pallidum* against

T. cuniculi. While the technic employed by Turner and his co-workers suggests some protection against heterologous organisms, it is difficult to determine the degree of such resistance.

MECHANISM OF IMMUNITY

The mechanism of acquired immunity in experimental syphilis is not clearly understood. In most instances search for the usual type of circulating antibodies has proved unsuccessful. It is true that reagin, the substance giving rise to positive complement fixation and flocculation tests for syphilis, is a circulating antibody but, as will be discussed below, its relation to the immune process is most uncertain. Tani⁴⁵ reported that agglutins for spirochetes could be demonstrated by the use of antigen from testicular emulsions to which had been added 0.5 to 0.7 per cent formaldehyde. These formaldehyde-treated emulsions of spirochetes presumably gave no spontaneous agglutination, showed no agglutination with normal rabbit serum nor with serum from animals infected with trypanosomiasis or relapsing fever. With syphilitic rabbit sera, however, definite agglutination occurred. In the experimental animal the titers of both the Wassermann reaction and the pallida agglutination reached their maxima four weeks after infection. In Wassermann positive human serums the agglutination tests were positive without exception whereas in Wassermann negative agglutination tests were usually showed negative. It is not now possible to assess the significance of these agglutinins in relation to the immune process. Confirmation and elaboration of Tani's work is indicated.

Ebersson,⁴⁶ Tani and his co-workers^{47,48} and Turner⁴⁹ demonstrated the presence of protective antibodies in the sera of immune animals and persons with late syphilis. Of the three, Turner's technic seems to be the most sensitive for demonstrating the presence of this protective substance. Nine parts of whole serum were combined with one part of spirochete emulsion, the mixture incubated at 37°C.

for six hours, and then inoculated intracutaneously on the backs of normal rabbits. The inoculated sites were examined daily for approximately forty days and differences in the size of the lesions noted. With emulsions exposed to immune serum, the incubation period of the lesions was prolonged resulting in no lesions or smaller lesions during the observation period. There seems to be little doubt as to the sensitivity of this technic in demonstrating differences between normal and immune sera, but it is difficult to determine what this test means in the way of absolute protection.

A most interesting demonstration of circulating antibodies was the parabiosis experiment of Tani and Aikawa.⁵⁰ The authors parabiosed ninety-one pairs of adult male rabbits, the duration of the parabiosis being from one to thirty-four days, averaging 12.8 days. Passive transmission to the partner of trypan blue, neoarsphenamine, Wassermann reagins, typhoid agglutinins and iodine were shown. In successful cases these were transferred to some extent at one to two days, in large amounts from four to five days and in the greatest amount in ten days. When the pairs made of one animal with late syphilis and one with fresh chancre lived more than ten days, a considerable degree of healing of the chancre was observed. The authors reported that the amount and strength of the spirocheticidal substance passively transferred were so great that large chancres were healed within a short time.

Passive transfer of immune antibodies from mother to fetus has not been demonstrated. Kemp and Fitzgerald⁵¹ inoculated thirty-one young rabbits born of syphilitic females. Twenty-four of thirty (83 per cent) developed primary lesions, seven had an asymptomatic infection and five were not infected. Presumably the inoculums used were relatively large, perhaps masking some passage of protective antibodies that might be demonstrated by a more sensitive technic.

The pathogenesis of the syphilitic infec-

tion has suggested that cellular factors might play a more important rôle in this immunity than humoral factors. Whether phagocytic mechanisms are involved is unknown. As reviewed by Chesney,¹ Levaditi⁵² and others believed that phagocytosis might play an important rôle in the immune process but this view has been opposed by Strempel⁵³ and others. Part of the difficulty may be technical since the staining methods currently available for demonstrating *T. pallida* may be inadequate to demonstrate phagocytized organisms.

An approach to the problems of a possible cellular immunity is found in the studies of Strempel and Armuzzi,⁵⁴ Tani and Aikawa⁵⁵ and Reynolds.⁵⁶ Strempel and Armuzzi⁵⁴ made subscrotal implants of testicular tissue, rich in virulent spirochetes, into previously infected untreated rabbits. Silver stains demonstrated that in the immune animals treponemes remained fixed at the site of inoculation, gradually disappearing, at first from the periphery of the implant and later from the centers as though by lysis. Within twenty-seven days after inoculation the sites of inoculation were spirochete free. In the normal control animals the spirochetes spread rapidly from the site of inoculation to the surrounding tissues. The experiments of Tani and Aikawa⁵⁵ differed in that they employed rabbits previously treated with neoarsphenamine late in the course of the immunizing infection. Their histologic findings were the same as those reported by Strempel and Armuzzi.⁵⁴ Both of these studies were based upon histologic examinations which depended upon silver stains for the demonstration of the spirochete. As Reynolds⁵⁶ points out, such studies were open to the objections that the staining methods were capricious and that occlusion of lymphatic channels from the preceding orchitis could not be dismissed as a possible factor in preventing the spread of the organism.

Reynolds⁵⁶ implanted testicular tissue infected with homologous strains of *T. pallida* into subcutaneous tissue of the thigh of immune and normal rabbits. At

intervals thereafter the implant was examined by darkfield and by transfer to normal animals. The inguinal lymph node was similarly transferred to fresh animals. In normal rabbits the spirochetes rapidly reached the regional lymphatics and remained motile in the implant for at least fourteen days. In the immune animals, however, the spirochetes could never be demonstrated in the regional nodes by node transfer and the organisms could be demonstrated in the implant by darkfield examination up to four days after implantation. The tissue implants remained infectious for only two days as determined by transfer to fresh animals. Reynolds concluded that in the immune rabbit the subcutaneously inoculated *T. pallidum* organisms of the homologous strain did not penetrate the lymphatics and were localized at the site of inoculation where they were subsequently destroyed by the immune mechanisms of the host. He further suggested that the actual immobilization and destruction of spirochetes was probably accomplished by local antigen antibody reaction as the immune antibodies were gradually in contact with the invading organisms.

Reference has been made to the relationship of reagin to the immune process. There is a growing body of evidence that reagin bears little if any relationship to immunity. Unquestionably, patients may be reinfected while their serologic tests for syphilis are still positive.⁵⁷ Large amounts of reagin may be formed in experimental animals without protecting the animals against syphilitic infection.⁵⁸ In the quantitative immunity experiments of Magnuson³⁸ the outcome of reinoculation bore no relation to the serologic titer of the immune animals.

Differences as to the relationship of allergy to immunity in syphilis are chiefly concerned with definitions of "allergy." As Rich, Chesney and Turner⁵⁹ have shown, allergy in the sense of hyperreactivity to the organism is not an essential part of the immune process in syphilis. Indeed, animals that are immune to a second inoculation

are extraordinarily passive to the presence of the organisms. Urbach and Beerman⁵ believe that immunity and allergy are both part of the same process. Since these authors include as allergy any altered reactivity on the part of the host, by their definition allergy does exist in these immune animals.

ARTIFICIAL IMMUNIZATION

Attempts to produce active immunity by artificial means have been uniformly unsuccessful. Suspensions of pathogenic *T. pallidum* have been killed by heat, by formalin and by lyophilization. They have been given in a single or multiple injections, over long and short time periods, with or without adjuvants and by many routes. Many of these technics have resulted in the development of positive serologic tests for syphilis in the serum of experimental animals but there has been no evidence of acquired immunity.

In a recent study Magnuson, Halbert and Rosenau⁶⁰ attempted to adapt Freund's adjuvant technic to the production of immunity against syphilis. Freund and his co-workers^{61,62} had employed the method to produce active immunity against malaria. Magnuson and his co-workers killed the Nichols strain of *T. pallidum* by lyophilization and incorporated the lyophilized spirochetes in a mineral oil emulsion with *Mycobacterium phlei*. Animals treated with this adjuvant technic developed positive serologic tests for syphilis but none became immune to even minimal infectious inoculums of the pathogenic spirochetes.

Similar results have been reported by Eagle⁶³ in which attempts were made to immunize rabbits by a wide variety of experimental technics. Again, many of these technics resulted in positive serologic tests for syphilis in experimental animals, yet challenging inoculation with minimal infectious inoculums showed no immunity.

DeLuca⁶⁴ treated twenty rabbits with heat inactivated Truffi strain of *T. pallidum*. Repeated injections of this vaccine had no effect upon the subsequent inoculation of virulent virus. Wakerlin⁶⁵ believed that

perhaps the failure successfully to immunize rabbits artificially might be due to the short treatment period over which such injections had been given. Accordingly, he attempted immunization of fourteen male rabbits by a total of sixty-five injections of 1 cc. each of organicluetin at four-day intervals. The total period of attempted immunization was 260 days. The organicluetin was essentially a phenolized (0.5 per cent) suspension of testicular tissue containing dead spirochetes in a physiologic solution of sodium chloride. It was heated at 60 degrees for one hour, incubated at 37 degrees for twenty-four hours, cultured to rule out contaminating organisms and subsequently kept at icebox temperature. This material contained from five to six dead *T. pallidum* per darkfield. None of the rabbits developed positive serologic tests for syphilis and none of the animals showed any immunity on subsequent inoculation of virulent organisms.

Levaditi and Lipin⁶⁶ prepared an emulsion of spirochetes by inactivating at a temperature of 55 degrees. This was then injected into rabbits subscrotally and intratesticularly. Neither immunity nor a positive serologic test for syphilis were produced. The same antigen was then given intravenously three or four times during a period of two to three months. In these animals the Meinicke test became positive. The subsequent challenge with virulent *T. pallidum* gave uniform infection.

Kolmer and Rule⁶⁷ reported similar unsuccessful attempts to immunize rabbits using heat killed formalized suspensions of testicular syphiloma.

IMMUNITY IN HUMANS

The extent to which findings in experimental animals can be applied directly to humans is unknown. As Chesney¹ indicated, much of our accumulated clinical experimental data antedates the identification of *T. pallidum* and modern technics for the laboratory diagnosis of syphilis. The early clinical experiments must be interpreted with some caution since the

diagnoses were not established on irrefutable grounds. Nevertheless, certain facts seem well established. Shortly after the onset of the primary lesion in humans a local immunity develops which prevents the development of a new lesion following reinoculation with *T. pallidum*. This failure to react is the "anergy" described by Neisser. This chancre immunity or anergy is relative since reinoculation with massive quantities of infectious material will result in a lesion.^{27,68} The duration of this anergy is open to some question. Several investigators have reported successful intracutaneous inoculation of patients with general paresis or tabes dorsalis.^{68,70,71} In an interesting experiment Prigge and Rutkowski⁷² demonstrated asymptomatic superinfection in a patient with late syphilis. Inoculation of a heterologous strain of *T. pallidum* failed to give a lesion but inguinal node transfer (to rabbits) was negative before the inoculation and was positive afterward.

Much of the current confusion in differentiating relapse from reinfection centers around concepts of immunity. With the introduction of any new form of syphilotherapy, enthusiasts are prone to call each recurrence a reinfection, thus supporting the adequacy of the particular type of treatment. The introduction of various rapid treatment methods for early syphilis has introduced new variables in the consideration of relapse versus reinfection. With present rapid technics the patient is given curative treatment early in the infection before an appreciable degree of immunity has developed. With the older treatment methods in which therapy was spread over a period of months or years, it was theoretically possible for the patient to develop some immunity during the course of treatment. The degree to which the smoldering infections resulting from subcurative doses contributed to the immune process is unknown although the work of Schamberg⁷³ would indicate that such subcurative therapy permitted immunity to develop. Schamberg's experiments were limited to rabbits given subcurative doses of fever or

nearsphenamine in the early stages of the disease. Subsequent reinoculation showed that these animals developed the same degree of chancre immunity as would have developed had their disease gone untreated. This suggests that the older type of treatment permitted a considerable degree of development of immunity during the course of therapy.

Increase in the number of reinfections cannot be attributed entirely to the changes in the immunity status. As Schoeh and others^{74,75} have emphasized, the use of the older long-term treatment kept the patient under effective prophylactic therapy during the time that he was circulating in the same sexual environment. The danger of reinfection from the original source was negligible by the time extended treatment was completed. With rapid treatment, not only may the patient be reinfected by the original source but the infection may be handed back and forth between partners as one and then the other is repeatedly treated, a situation which has been aptly termed "ping pong" syphilis.⁷⁴

One cannot now ascertain the extent to which either changes in immunity or in sexual environment may influence the current apparent failure or relapse rates in clinical syphilis. If acquired immunity in man develops in a progressive manner similar to that in the rabbit, one would expect that a previous infection with syphilis would modify a subsequent exposure to the disease. If the original disease is treated early, one would expect the majority of reinfections to take the form of symptomatic reinfection. If reinoculation occurs at a later date, an increasing proportion would take the form of either asymptomatic reinfection or no infection whatsoever. Such asymptomatic reinfections may or may not be associated with apparent serologic relapse.³⁷

The degree to which so-called serologic relapses may actually be due to asymptomatic reinfections was first discussed by Chesney and Kemp.³⁶ It was their experience that the majority of the animals de-

veloping asymptomatic reinfection at the same time had a serologic relapse. As was indicated above, Magnuson³⁷ found that if the immunizing infections were of longer duration, such asymptomatic reinfections occurred without change in the serologic titer. It is possible that a considerable proportion of the presently observed serologic relapses which are attributed to treatment failure may actually represent asymptomatic reinfection in humans. There are at the present time no clinical means of differentiating the phenomena.

It has been commonly accepted in clinical literature⁷⁶ that "serologic relapse" followed by the development of a new darkfield positive lesion in a patient previously treated is a clear cut indication of relapse from the original infection. Magnuson³⁷ has shown that in the experimental animal an identical sequence may be produced by reinfection. Rabbits cured of the original infection may be reinoculated with virulent spirochetes; and in spite of the fact that the site of inoculation is examined frequently and carefully, serologic titer may increase before the clinical lesion becomes evident. The possibility, as yet unproved, that this sequence may occur in man suggests caution in the unqualified acceptance of the current clinical belief.

In the present absence of adequate clinical criteria to differentiate relapse from reinfection it would appear that an epidemiologic approach would offer the most immediate information as to the relative frequency of the two phenomena. Through comparison of apparent cure rates in different population groups known to differ in promiscuity, it may be possible to assign the differences in apparent cures to reinfections. Such conclusion would rest on the assumption that the two groups did not differ in the absolute "curability" of their syphilis and that acquired immunity developed at the same rate in the two groups.

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The Epidemiology of Syphilis^{*}

With Particular Reference to Contact Investigation

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EPIDEMIOLOGY is the study of disease and the circumstances under which disease occurs, the study of multiple causes of and reasons for disease incidence and prevalence. According to Munson¹ an epidemiologist is "that creature who curiously combines a reasonable skepticism and insatiable curiosity with a passion for the truth, and has the ability to recognize the truth when it looks him in the face and, with all of this, has the initiative to apply sufficient sole leather to the job to get the facts."

Clinical medicine is concerned with disease as it affects the individual while epidemiology is concerned with disease as it affects aggregations of individuals. Clinical methods have their origin in the basic sciences and are utilized to study the changes in, and determine the extent of damage to a single unit of a population. On the other hand, epidemiologic methods, stemming from the same basic sciences, investigate disease causation, the frequency of occurrence and modes of spread of a disease in the population as a whole. The first leads to an understanding of pathogenesis and ultimately to appropriate treatment of the individual. The second leads to an understanding of the principal factors concerned in community disease prevention and in intelligently directed community control efforts.

Reference to medical literature discloses innumerable titles of papers and books referring to epidemiology as applied to syphilis. These represent a variety of viewpoints as to what constitutes epidemiology

in this field, such as: (1) prevalence and incidence studies;² (2) contact investigation and related case-holding;³⁻¹³ (3) case-finding methods in general;¹⁴ (4) duties of personnel and details of the control program;^{15,16} (5) patient education;¹⁷ (6) conjugal syphilis;¹⁸ (7) studies of localized outbreaks;^{19,20} and (8) broad principles of the science of epidemiology as applied to the disease.²¹⁻²⁴

The present paper examines the subject from this last viewpoint in order to show the need of careful attention to the basic knowledge of epidemiology in syphilis control.

At any time the status of syphilis control in a community will depend entirely upon the ecologic relationships (brought about by whatever means) which exist among the causative agent, the human host and environment.^{21,25} An appreciation of the relationships of these three factors is essential for an understanding of incidence and prevalence, for effective contact tracing (so-called "applied" or "practical" epidemiology) and other case-finding measures and for intelligently directed control efforts. These factors are so closely related that changes in one directly influence some phase of both of the others. The *organism* itself may change as a result of its relationship to the host or to the environment (mutations, variations, adaptations). The *host* may vary in the degree and type of reaction to the organism as a result of intercurrent infection or disease or of food deficiencies. The relationship of one host to another may depend upon the extent of crowding, the stresses

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of life, certain habits and customs of the people. Changes in the *environment* may result from man's purposeful regulation of his own surroundings. Certain important features of our present knowledge of organism, host and environment as they relate to syphilis will be reviewed briefly and considered in the light of practical application to syphilis control.

NATURE AND CHARACTERISTICS OF THE SPECIFIC MICRO-ORGANISM

There is little doubt that the *Treponema pallidum* is the cause of syphilis. Its infectivity and pathogenicity for man and certain laboratory animals have been proven conclusively. Yet considerable uncertainty concerning the authenticity of the cultivation of the organism on artificial media in a form virulent for animals has left Koch's postulates unfulfilled.

Its characteristic morphology and motility²⁶ are well known, yet its relationship to the organisms of yaws, bejel and pinta has not yet been clarified. No student of the disease should fail to read the discussion of these relationships in the review by Hudson.^{27*} The biology of this organism and the evidence relating to its possible life cycle and virulent granular form have been reviewed by Ingraham.²⁸ The biologic requirements of the *T. pallidum* explain why syphilis is a disease of intimate contact. This organism is a very fragile one, unable to resist drying, unfavorably affected by many common agents, and is said to be killed by the weakest antiseptics and to be killed more quickly by soap solution than by many strong disinfectants.²⁹ It dies under blood bank conditions in seventy-two hours³⁰ but will survive rapid freezing to -76°C . for a year.³¹ It has been found infective for twenty-six hours in syphilitic autopsy material.³² It is immobilized at 41°C . (105.6°F .) in two hours. These facts have a direct bearing upon the behavior of the organism in nature. Only on the mucous membranes about the genitalia and in the mouth are conditions consistently found in man which

permit its survival for periods long enough for invasion. In the rabbit it has been shown that the spirochete can penetrate intact mucous membrane and produce infection.³³ Infection by penetration of intact human skin or mucous membrane has never been demonstrated. The *infectivity* of the organism is demonstrated by its ready adaptability to human and certain laboratory animal tissues. A single organism may produce the disease in animals.³⁴ It may be produced experimentally into a number of animals but there are no known vectors in nature and no reservoir hosts other than man. It is an outstanding example of parasite adaptation. Its *pathogenicity* is shown by the fact that it provokes tissue reactions in man, rabbits, monkeys and other animals. In the rabbit, and perhaps in man, the presence or absence of early lesions depends upon the number of organisms inoculated.³⁴ In mice the infection is usually entirely symptomless and the organism is recovered only by tissue transfer to rabbits. Its *virulence* is established by the fact that it is capable of producing severe clinical reactions in the skin, bones, heart, blood vessels and in the nervous system. Evidence of its *antigenic* power is its capability of producing immunity³⁵ and the fact that it calls forth the production of an antibody-like substance (reagin) which is essential for serologic diagnosis.

Thus, we have a virulent, fragile, characteristically motile organism as yet not cultivated on artificial media, indistinguishable morphologically from the organisms of three related diseases, unproven as to life cycle, of considerable infectivity, pathogenicity and antigenic power. A knowledge of the biologic characteristics of this organism is essential to an understanding of its mode of spread and of its control in an individual or in a community. As stated by Stokes,²⁹ "It is not a divine moral purpose, or a satanic punitive ingenuity that connects syphilis with genital activities, but a mere biological accident no more significant in the last analysis than the fact that potatoes grow in sandy loam." These

* Also see Hasselmann.³⁶

biologic requirements are the characteristics which: (1) determine the reservoir of infection; (2) dictate the means of transmission; and (3) contribute to the host-parasitic interaction.

HABITS AND CHARACTERISTICS OF THE HOST

The human host is the sole reservoir of syphilis infection. In nature syphilis has been found only in the human species. The infection can be transmitted artificially to certain animals but it dies out spontaneously without propagation to others of the same species. Whether or not man, as the reservoir of the disease, transmits it to others depends upon: (1) the outcome of the complicated host-agent interreaction and (2) the habits and customs of the population.

Reaction between the Human Host and the Treponema Pallidum. This interaction determines the clinical stages of syphilis infection and is best described in terms of the biologic course of untreated syphilis.³⁶ From the epidemiologic point of view the most important phases of this biologic course are those clinical stages during which it is possible for one case to give rise to another. In acquired syphilis this infectious period is limited to early acute stages of syphilitic infection and is terminated by treatment or by the spontaneous development of resistance on the part of the host. When lesions begin to heal, infectiousness diminishes. Eventually the organism is limited to a few isolated foci not located on body surfaces. Nevertheless, during the first few years of the disease, this "immunity" may break down with the result that infectious lesions recur. Under such circumstances the patient is capable of transmitting the disease to others.

Under certain conditions the syphilitic pregnant woman can transmit syphilis to the fetus *in utero* after, but not before, the fourth month of pregnancy.³⁷ Cellular as well as humoral factors within the host are thought to be responsible for this fact. Transmission to the fetus depends upon

the duration of infection in the mother, the number of previous pregnancies and the amount and type of treatment given. A child of a treated or untreated syphilitic mother may be born: (1) non-syphilitic with a negative serologic test or a positive one which becomes negative in a short time; (2) syphilitic with a negative or positive serologic test and no signs of the disease until several weeks after birth; (3) syphilitic with a positive test and with signs of the disease at the time of delivery; or (4) dead as a result of syphilis infection.

In acquired syphilis when the *T. pallidum* comes into relationship with a new host: (1) the organisms may fail to gain access and lodgment; (2) they may gain access, lodge, multiply and produce infection, without early discernible tissue reaction (symptomless infection); or (3) they may gain access, lodge, multiply and produce the characteristic discernible reactions of early syphilis. This early tissue reaction (primary and secondary syphilis), when it occurs, is usually mild, superficial, non-destructive and heals spontaneously in days or weeks without scarring. An indeterminate period of clinical latency (weeks to years) follows without outward signs of infection during which the infected individual is recognized as syphilitic only by means of positive blood serologic tests. This period may be interrupted during the first few years by recurrences of infectious lesions representing renewed spirochetal aggressiveness—secondary relapse or recurrences in skin, mucous membranes, eyes or central nervous system. After an unpredictable number of years late non-infectious tissue reactions may occur in skin, mucous membranes, cardiovascular, nervous and other systems.

The host reacts to the presence of the organism by developing a state of immunity or resistance which influences the spontaneous healing of early lesions, protects against new organisms introduced from without,³⁸ withstands to a variable degree the aggressiveness of the organisms present in the tissues and in most instances main-

tains clinical latency throughout life.^{39,40} There is some evidence that such host factors as sex,⁴¹ pregnancy,^{42,43} race⁴⁴ and constitution⁴⁵ affect this host-organism relationship.

Thus, transmission of syphilis depends not only upon satisfying the biologic requirements of the organism and the habits and customs of the population but also upon certain conditions of the host-parasite relationship. This relationship must be such that: (1) it is possible for the organism to escape from the infected host in sufficient numbers; (2) the organism must be appropriately transmitted under conditions which satisfy its biologic requirements; and (3) it must gain access by finding appropriate portals of entry in the new host. Moist surfaces provide the avenues by which the organisms escape from their reservoir, and intimate contact by sexual intercourse or kissing furnishes the conditions necessary for conveyance to a corresponding portal of entry in a new host. The newly implanted micro-organism becomes established under conditions of moisture, warmth and low oxygen tension and may penetrate intact mucous membrane.³³

Moist infectious lesions are present only during primary, secondary and recurrent secondary syphilis. Body fluids and secretions (saliva,⁴⁶ semen,^{47,48} usual common vaginal discharges⁴⁹) from syphilitics in various stages of the disease have been studied experimentally and frequently have been shown to contain the organisms during the early stages of syphilis when lesions are present, but only rarely, if ever, during the later stages when there are no obvious lesions. Blood is a passive carrier of the organisms⁵⁰ and has been shown to be infective chiefly during the incubation period⁵¹ and while primary and secondary lesions are present. Transfusion syphilis⁵² has resulted when the donor had early lesions or in the period before their occurrence or immediately after their disappearance. The usual explanation of *in utero* infection at the present time is that occasional spirochetemia occurs and results in the circulatory transfer

of organisms to the fetus. This has not been proven experimentally.

Intimate contact with primary and secondary lesions provides the most favorable conditions necessary for transmission. However, despite the presence of infectious lesions transmission following unprotected sexual exposure does not invariably take place.

Klingbeil and Clark¹⁸ found that eighteen of ninety-seven marital partners (18.6 per cent) escaped infection although they were exposed sexually to early infectious lesions. Other studies of conjugal syphilis have contributed to the knowledge of transmissibility. O'Leary and Williams³³ found that very few marital partners had become infected when the interval between infection and marriage was more than five years. Klingbeil and Clark found no instance of conjugal infection among spouses of twenty-five patients (thirteen untreated) who had acquired syphilis four or more years before marriage.

Transmissibility, therefore, depends upon: (1) the duration of infection; (2) the presence of moist lesions; (3) the infectiousness of secretions; (4) tissue reservoirs of organisms; (5) intimate contact with the organism in sufficient numbers; and (6) accessible portals of entry in the susceptible individual which satisfy the biologic requirements of the organism.

Habits and Customs of the Population. The chance of exposure to any parasitic organism is dependent upon habits and customs of the people and upon their social and economic environment. The type of epidemiologic attack to be employed depends upon the nature of the total community syphilis problem. This is influenced by the sexual behavior and promiscuity of the population. High prevalence and high incidence rates usually are a reflection of high promiscuity rates since the frequency of infection varies directly with the frequency of exposure to the *T. pallidum*.

Measurement of the Reservoir. The number of persons comprising the syphilis reservoir varies from time to time, depending upon

the balance between increments of new infection and decrements by cure or death. Two fundamental statistical concepts must be differentiated in measuring this balance. The first of these concerns the number of new infections occurring during a given period of time, which when related to the number exposed to risk of infection is expressed as the *incidence* or attack rate (e.g., the statement 1.4 per 1,000 *per year* is one of incidence). The other concept represents a static rather than a dynamic phase. It concerns the number of infections that exist at any one time, and when related to the number of persons exposed to risk of infection is expressed as the *prevalence* rate (e.g., the statement 1.4 cases per 1,000 population is one of prevalence). Despite their differences these two concepts, incidence and prevalence, are not independent of each other. Prevalence at any time is the result of a previously operating incidence or attack rate.

Since crude rates vary according to race, sex, age, social and economic status of the population, specific rather than crude rates should be computed for valid comparison. Rates for negroes are higher than those for whites; for example, among men of draft age⁵⁴ the total syphilis prevalence rate of 47 per 1,000 completely concealed the fact that the rate for negroes was 272 per 1,000 and that for whites 23.5 per 1,000. Among negroes the total rates for men and women are approximately the same; but there is considerable variation according to age, the rates for women being higher than those for men before the age of twenty-five, and those for men higher than those for women after the age of thirty. Among whites men have a higher total rate than women while women have a higher rate than men before the age of twenty-five. Incidence is higher in young persons than in old, while prevalence, representing an accumulation, is higher in older persons.

Adherence to these underlying principles of measurement constitutes a fundamental part of the epidemiologic description of syphilis.

ENVIRONMENTAL CONDITIONS

The influence of any one of a group of environmental factors cannot be measured with precision, but specialized studies have been made from time to time on one or another aspect of environment as it relates to syphilis; for example, geography and climate and syphilis,^{2,27,55} occupation and syphilis,^{56,57} wages and syphilis,^{58,59,60} material standards of living and syphilis,⁶¹ education and syphilis,⁶¹ syphilis and the law^{62,63} and syphilis and war.⁶⁴ It is generally understood that environment is not merely physical surroundings—topography, climate, soil, water, plants, housing, etc.—but that the population (society) itself is part of the total environment. This is the social environment and from it forces arise which may influence the occurrence of syphilis to an even greater degree than do those from physical surroundings.

APPLICATION OF EPIDEMIOLOGIC PRINCIPLES

The object of epidemiology is to determine the details of relationships that exist among the various causes of disease so that means may be developed to alter this relationship in a direction that will be favorable to the human host. This objective in syphilis can be attained only by a reduction in the number of effective exposures to the *T. pallidum* since it is not possible to eliminate intimate contact, to immunize nor to practice mass quarantine. At least four methods of reducing effective exposure are available: (1) reduction in the total number of exposures by decreasing promiscuity; (2) prophylaxis; (3) maintenance of adequate treatment and post-treatment examination requirements among discovered or known infections; and (4) reduction of periods of infectiousness by earlier recognition of undiscovered infections. The first method includes the suppression of prostitution which is a function of law enforcement and the reduction of promiscuity by sex education. The second method is a medical function and the third and fourth are epidemiologic responsibilities.

The reservoir of syphilis infection comprises two groups: *discovered infections* and *undiscovered infections*.

Discovered Infections. In any schedule of treatment requiring more than one visit for treatment or post-treatment examination, case-holding is of paramount importance.^{65, 66, 67} Case-holding begins with the patient's first medical contact. The informed patient cooperates; the confused or perplexed patient fails to carry out treatment and post-treatment examination schedules. On the other hand, the most completely informed patient may be expected to neglect treatment and post-treatment examination in the face of rough or discourteous handling, lack of privacy or poor technics which cause pain. Both the control of the discovered case and the discovery of related new cases depend upon the patient's understanding of the illness and its implications since it is the patient who will lead to many of these undiscovered cases. It is upon the patient that we depend for the name and location of his contacts. It is the physician's responsibility to explain the disease to each patient in understandable terms: the reason for taking treatment and for post-treatment examination; his outlook with and without treatment; his potentialities for cure, etc. According to Ingraham,⁶⁸ "The initial interview with the discovered case is the foundation of all of our hopes for success with the individual who has syphilis. It involves an interpretation to the patient which will enable him to accept syphilis as his present illness. It is the basis for his observance of infectious precaution. It is an attempt to forestall his lapse from treatment (or follow-up).^{*} It may uncover personal problems that limit his ability to undertake the treatment (or follow-up).^{*} It prepares and often completes the necessary arrangement for the examination of contacts. In fact, I suggest that the intelligent interpretation of syphilis may even mean the beginning of effective person-to-person propaganda for the control of this disease." This is the physician's responsi-

bility. In discussing these problems with the syphilis patient it must be remembered that before he was a patient he was the public; even before that he was an ordinary individual who was susceptible to all the cares, worries and conflicts of any other individual in the population and now has an additional burden which needs explanation and care.

Undiscovered Infections. The great volume of undiscovered infections is largely responsible for perpetuation of the disease. Case-finding procedures planned with intelligent case-holding objectives in view are the basic fundamentals of syphilis control. Case-finding, although it is one of the fundamentals of the program, is not an objective in itself. To be of benefit to the community, it must lead to: (1) better understanding of the prevalence and incidence of the disease; (2) protection of public health or promotion of public safety; and (3) the treatment of the infected.⁶⁹

In general, thorough case-finding is the result of: (1) a high index of suspicion and judicious use of all diagnostic measures; (2) proper application of so-called mass blood testing procedures (screen examinations or screen testing); (3) carefully planned and executed public information programs; and (4) contact investigation.

The choice of a case-finding method will depend upon prevailing infection rates in the community and available facilities.^{70, 71} Contact investigation is the most direct epidemiologic approach and offers the best opportunity for discovering early infectious cases.⁷²

Contact Investigation. Contact investigation starts with the infected patient and proceeds cautiously into the home or the community where that person may have acquired the disease and where he might have transmitted the disease to others. It seeks to discover infection among *all* of his intimate contacts as early as possible and to discover infection previously overlooked or dismissed as trivial. The ultimate value of contact investigation is in direct proportion to the length of time by which the

^{*} Parenthetical expression is the present author's.

infectious period is shortened in those contacts who have syphilis. Thus, accomplishment is not measured by the number of contacts examined and treated but by the degree of success in materially shortening the contacts' period of infectiousness. As pointed out by Ingraham,⁵ if further transmission of the disease is to be prevented, the patient must be treated early, he must have some idea as to the whereabouts of his sexual intimates, he must be willing to divulge this information, the alleged contacts must be identified and located, they must be persuaded to submit to medical examination and, if infected, they must submit to treatment and further query.

In spite of these multiple barriers to successful contact investigation, case-finding by this method should be simple since investigation is limited to a relatively few persons with whom the patient has been in intimate contact. Patients are willing, under proper circumstances, to divulge information concerning these intimate contacts, and the contacts in turn are willing to submit to medical examination if they are approached in a suitable manner. A patient can be expected to withhold information about his intimate contacts because he may be ignorant of the potentialities of the disease. The physician, on the other hand, is fully aware of these potentialities and it is his obligation to inform the patient of the dangers of the disease to himself and to his contacts. Failure to participate in this manner in contact investigation is failure to assume a medical responsibility. The average physician is understandably more concerned with the confidential relationship which should exist between patient and doctor than with the effect of the disease problem in the community. He finds it hard to accept measures which might shake the patient's trust in him; however, it has been shown that successful participation of the private physician in this phase of syphilis control is practicable.^{73 74}

Numerous reports of methods and results of contact investigation have come from private and public clinics throughout the

country and from both federally and locally operated Rapid Treatment Centers. That such an approach in case-finding is practical and productive has been proven conclusively and repeatedly in the periodic Statistical Letters and Epidemiologic Reports of the United States Public Health Service and in papers by Brumfield and Smith,⁷⁵ Casselman and Cadwallader,⁷⁶ Clark,⁸ Clark and Sargent,⁷⁷ Dyar and Guthrie,⁷⁸ Dyar and Goodwin,⁷⁹ Easley, Parkhurst and Swank,⁸⁰ L. Ingraham,⁶⁸ N. R. Ingraham, Jr.,⁵ Nelson,⁷³ Rosenthal and Weinstein,⁶ Smith and Brumfield,⁸¹ Smith and Sheppe,⁸² Turner, Gelperin and Enright,⁸³ Webster and Shelley,⁹ Weinstein⁸⁴ and many others. Until recently no uniformly applicable index of appraisal of the results of various methods has been available. One index, first suggested by Turner, Gelperin and Enright,⁸³ was expressed in terms of the number of new infectious cases found per one hundred original patients with primary and secondary syphilis. No weight is given to the time element in this index. Recently, Iskrant and Kahn⁸⁵ defined the following appropriate indices of accomplishment which have been given considerable trial on a national scale: the contact, epidemiologic, brought-to-treatment and lesion-to-lesion indices. The last index qualitatively evaluates extent of community exposure since it is related to contacts with lesions. It indicates that the period of community exposure was interrupted by treatment of contacts during actual infectiousness. Early interruption of infectiousness is not reflected in this index as it is now used.*

Iskrant and Rion⁸⁶ analyzed accomplishment in contact investigation as reported by health agencies in twenty areas during the period, July to December, 1946, utilizing these indices. In these areas the range in *contact index* was from .87 to 3.31 contacts named per original patient; the *epidemi-*

* Dividing the "lesion-to-lesion" index by the average number of days that infectious lesions were present in the contacts before examination would take the time factor into consideration—the earlier the examinations the higher this rating—and permit comparisons of effectiveness of the investigations.

ologic index from .34 to .84 infected persons identified through contact investigation per patient with early syphilis; the *brought-to-treatment index* from .11 to .57 hitherto unknown cases found per original case; and the *lesion-to-lesion index* from .03 to .39 contacts with lesions present per original patient with lesions.

Some of the papers mentioned give sufficient data for the calculation of these indices for individual clinics. The range of the *contact index* was between 1.1 and 2.9; of the *epidemiologic index* between .23 and 1.28; of the *brought-to-treatment index* between .12 and 1.00; and of the *lesion-to-lesion index* between .06 and .72.

A variety of technics and methods was used by these investigators. Poorst results follow the use of compulsion. Success depends primarily upon the proper persuasive approach to the original patient.⁸⁷⁻⁹⁰ The key to success lies in his attitude; he alone can identify his contacts; and it is he, not the physician, social worker, nurse or investigator who actually formulates the type of method to be employed in locating contacts. Before the patient is willing to disclose the secrets of his intimate relationships, a good rapport must be established between him and the questioner. Direct questioning should be avoided until the patient has an intelligent understanding of syphilis and its implications insofar as he and his health are concerned. The means of spread from person to person must be explained. It should be pointed out to the patient that no attempt is made to determine who acquired the disease first, patient or contact; that the original patient merely serves as an index to the discovery of many others suffering from the same disease and capable of transmitting it.

In contact investigation attention is focused in two directions: toward the patient himself and toward the contacts named by the patient.

Approach to the Patient. The differentiation of "source" and "spread" contacts should be discouraged. The expression "source of infection" carries implication of

accusation and should be avoided purposely both in the approach to the patient and to his contacts. Fixing the blame is unimportant since each infection is a potential source of another one. The patient when asked, "Where do you think you got this?" or "Who gave you this disease?" thinks in terms of his most recent exposure, or of a consort he suspects or dislikes, or about whom he has heard rumors. He thinks in terms of a single individual or a single exposure since (presumably) he has been informed prior to this questioning that the disease is spread from one person to another through intimate contact involving moist surfaces. He is asked to make a decision which, because of the variation in incubation period, is difficult or even impossible for the trained physician. This question also allows the patient to maintain the concept of being wronged or of having wronged someone else. The attitude of "source of infection" in the approach to the contact places him or her on the defensive. It may sanction an erroneous impression on the part of the investigator that the "alleged" source is really the guilty party and as such is not deserving of persuasive tactics. An inexperienced worker may think that the work is done and the task is complete when this "source" is found, yet every infected person is a potential source of another infection. The question, "Where did you get it?" implicates only one person and ignores those exposed to the patient's own infection. It does not answer the basic epidemiologic question, "Who has been exposed to syphilis?" nor does it allow maximum epidemiologic attack. If further transmission of the disease is to be arrested, information must be sought concerning *all* sexual contacts over intervals selected to include both the stage of active communicability and the incubation period of the disease. These intervals have been variously defined but, in general, examinations should be made of all contacts of the three-month period prior to the appearance of a chancre or the four to six months prior to the onset of secondary manifestations. Examina-

tion of contacts (other than marital and family) of patients with syphilis of more than twelve months' duration contributes little to the control of the disease. Time magnifies the difficulties in finding them and, when found, their period of communicability has already been interrupted by the natural course of the disease.

The married patient presents the first vital problem, that of the interpretation of the diagnosis to the spouse. The emotional reaction on the part of the patient may be one of self-condemnation or spouse-accusation. In either event, the patient must be convinced of the necessity for examination of the marital partner. Although it is more desirable for the patient to assume the responsibility of telling the marital partner, valuable assistance can be rendered the patient by a discussion of methods of communicating the information. The decision of what to do under this circumstance will depend upon the degree of mutual understanding that exists between the patient and the spouse and the available facilities of the clinic to carry out the most advantageous approach. The patient may be advised as to what to say, may bring the spouse in for discussion with the physician or clinic worker or in some instances the "family approach" may be used. This approach has been effectively used and described by Sweeney.¹³ It is accomplished by means of a pre-arranged plan with the original patient. After the diagnosis of the original patient has been made, it is planned that a representative of the physician or clinic will call upon the original patient and the spouse, informing them simultaneously that both have been exposed to syphilis (which indeed is the truth if one of them has the disease) and that both should go for examinations. Certain disadvantages of the plan cannot be denied. It is true that pre-existing suspicions may be confirmed and further marital discord stimulated or new suspicions aroused. Nevertheless, a desire to maintain an intact family unit is the rule and in this approach no accusation has been leveled at either of the marital

partners. There is no indication that infidelity of one of the partners is known or suspected; "face" is saved.

The least desirable decision of all is to have a spouse examined under some unrelated pretext. The disadvantages of this are apparent. In most instances if the patient has early syphilis, the spouse will also be found to have early syphilis if exposure has taken place. Therefore, if the spouse examined under some other pretext is found to have syphilis, the problem of family relationship remains to be solved. If, on the other hand, *repeated* examination fails to disclose syphilis in the partner, the original patient is committed to a life of fear of being found out. From time to time reasons for further examinations, blood tests and lumbar punctures must be explained by the patient to the uninfected, unsuspecting spouse.

To prevent premature marital accusation, it is well to remind the patient that the spouse may be found *not* to have syphilis or that, if infected, the blame may fall on the one whose infection was discovered first.

The necessity for the examination of other members of the family depends upon their habits and the possibilities of effective exposure. Syphilis is a disease of intimate contact. There is little or no danger to other members of the family through casual contact even when lesions of primary and secondary syphilis are present. However a nursing child of a syphilitic parent needs examination. Because of family habits of promiscuity, adolescent siblings of unmarried patients with primary and secondary syphilis provide a high yield of new cases of early syphilis.⁸

Obtaining Names of Non-marital Sexual Contacts. When patients have been convinced of the good fortune of early diagnosis and when they realize that they can be responsible for others deriving similar benefits without identifying themselves, they usually can be persuaded to divulge the names of their sexual contacts. Usually it is necessary to emphasize the fact that all persons with whom they have had intimate

contact may have the disease without knowledge of infection or even of exposure to the disease. The responsibility of protecting these unsuspecting persons from the late manifestations of syphilis is placed directly upon the patient since the patient alone knows of the exposure to the disease. The patient is reminded that failure to diagnose and treat these contacts is failure to prevent blindness, insanity and perhaps death and his contribution to this failure is emphasized. In seeking contact names, great care must be exercised not to allow the patient to think in terms of the one who infected him nor that he is being accused of infecting others.

Patients who have disclosed the names of their sexual consorts under a promise that their own names will not be disclosed should be warned of the possibility of inadvertent revelation of their secret. Their contact may, after being seen by the investigator, canvas all the friends in order to determine "who gave the name." It must be impressed upon the patient that if approached by the contact, it is not because of knowledge but because of suspicion only.

To the patient who gives no contact names or who admits one or more contacts and withholds the names of others, promising personal attention to the matter, the question should be asked, "What are you going to tell them? How are you going to impress upon them the importance of examination without disclosing your own diagnosis?"

As much information as possible should be obtained about the contact. Ideally, the full name and address, marital status, size and description of family and information on the home situation should be obtained. When this is not obtainable, other helpful data are nicknames, description, height, color of hair, approximate age, distinguishing physical characteristics that may be visible, habitus, places where they might be found in addition to home, some description of the surroundings of the home if the address is not available (fence, steps, type of door, type of porch, size of house, near

corner, away from corner, on the hill, in a valley, near a track, etc.). The marital status and other family data of the alleged contact should be noted as well as other possible personal information that may assist in persuading the contact to come in for an examination. The patient should be asked if he or she is aware of the alleged contact attending other clinics or visiting private physicians.

Approach to the Contact. This may be made: (1) by the patient or (2) by the treating agency or its delegate. There are both advantages and disadvantages in permitting the patient to persuade the contact to come in for examination. The advantages are financial. The disadvantages are that the patient usually will not be able to emphasize fully the importance of examination, that there may be a considerable delay in securing the examination and that the contact learns of the patient's infection. The patient who volunteers to bring his contact in may not realize that this automatically divulges his diagnosis. He should be advised of this fact.

There are several types of approach to contacts when carried out by the treating agency or its emissary, such as: (1) by telephone, (2) by letter and (3) by personal visit.

The use of telephone messages, letters, cards and telegrams for persuading contacts to come in for an examination requires knowledge of the home situation of the contact. These vehicles should be directed in such a manner as to ensure that the contact gets an adequate message without exciting the curiosity of others in the family. The results of the use of telegrams, special delivery and registered letters as compared to visits has been studied by Bundesen, Bauer and Baker,⁹¹ by Rosenthal and Kerchner⁹² and by Koch and Thornton.⁹³ The content of these messages varies but it is the general consensus that they should *not* contain a statement concerning syphilis or exposure to it. They should be strong enough to impress upon the recipient that it is absolutely essential to come to the

doctor, a specific clinic or the health department for a discussion of the contents. Various subterfuges have been used including letters with insufficient postage to create an interest and, in one instance, Brumfield, working in New York State, is said to have sent a blank envelope addressed to contacts hoping that its emptiness would persuade them to come quickly to the point indicated in the upper left hand corner of the envelope.* There is no information as to the success of this subterfuge.

Personal Visits to Contacts. For the purpose of defining methods of approach, contacts are divided by Sweeney into three groups: (1) the independent single person, (2) the minor living with the family and (3) the married person. The independent single person who has been named as a contact presents little difficulty. There is considerable difficulty in planning the course of action to secure the examination of a dependent minor named as a contact. A decision must be made as to whether the minor should be appealed to individually or through the family, whether or not the minor should be protected or exposed or whether the so-called family approach might be used. There are similar difficulties in arranging examinations for contacts who are married and living with marital partners. A choice must be made between interviewing secretly and individually, or interviewing the two marital partners simultaneously in the manner described in the discussion of spouses of patients. The individual approach has the advantage if the contact is free of syphilis, but it is a great disadvantage if the contact is infected, since the problem of breaking the news to the spouse still remains. The probability of the contact being infected is about three to four.⁸ The family approach has been used with considerable success by Sweeney working in the clinics of the Vanderbilt University Hospital.

Although the content of the interview with the alleged contact may vary considerably, the following general pattern is

* This has not been verified.

suggested. After proper introduction, the investigator can explain the visit something like this: "Whenever we see at our hospital (or clinic or health department) a patient with any kind of catching disease, such as tuberculosis, measles, scarlet fever, typhoid, syphilis or smallpox, we ask them to tell us the names of all the people in their families and others that they have been 'close to' during the time that the disease was catching. We do this so that people who might have caught the disease may have opportunity for examination before the disease has gone very far. You will agree that this is a good idea, won't you? Now, a short time ago, we had a patient at our clinic who was found to have catching syphilis. Do you know what syphilis is? (And then follows, depending upon the reply, some information about syphilis.) We asked this person to give us the names of members of the family and persons that they had been 'close to'* so that we could go out and see that these people were examined. Among the names that were given us was yours. The patient wanted to protect you from the serious effects of the disease and thought enough about you to want to help you." To the inevitable question of who that person was can be given the answer that the investigator does not know, or that the investigator is maintaining a confidence. This impresses upon the contact that confidence will be respected. In the great majority of instances this explanation is satisfactory. Ample opportunity is available to explain syphilis to the contact, to impress upon him the importance of immediate examination and to point out the possibility of syphilis being present without symptoms. The contact is then encouraged to go to his private physician or to a clinic for repeated blood tests and physical examinations.

It should be re-emphasized that the period of time between the diagnosis of syphilis in the original patient and the examinations of contacts is extremely im-

* Note here that sexual intercourse is not mentioned and the sex of the original patient is not revealed to the contact.

portant in the spread of syphilis. Intelligent explanation to the contact by experienced workers shortens it. The use of any method of communication with the contact is limited by existing facilities and by the completeness of information about the contact. Guthrie⁹⁴ has shown that effort expended on contacts for whom identifying information was incomplete increased several fold the cost of case-finding. Since the epidemiologic attack is concerned with mass phenomena, methods must be utilized which give maximum numerical returns for the effort expended. Thus, only a limited amount of effort can be allowed in the individual case.

Once the contact reaches the physician or clinic, he becomes a challenge in case-holding because examinations must be repeated periodically throughout the probable incubation period of syphilis, and in case-finding, because all available diagnostic measures must be judiciously utilized. Moore⁹⁵ summarizes the situation: "Organized case-finding by routine serologic testing and the epidemiologic approach offer a solution of many of the difficulties encountered in getting patients under treatment. If they are generally applied, the demand for treatment facilities would be from two to three times greater than at present.

"To the factors enumerated which operate to prevent persons infected with syphilis from seeking early and adequate medical care, that is, symptomless infection, ignorance, carelessness, viciousness, and the easy access to quack or drugstore treatment, may be added one other factor which applies to early and late syphilis alike; namely, the ignorance of many physicians of the elementary methods of recognizing syphilis. Unfamiliarity with the darkfield apparatus, a lack of understanding of the proper use or interpretation of serologic tests, and an absence of appreciation of syphilis as an infectious disease—these are the blinders which hamper the medical profession."

SUMMARY AND CONCLUSIONS

Knowledge of the basic facts of the epidemiology of syphilis is essential for its control. These basic facts are acquired through careful study of: (1) the biologic characteristics of the *T. pallidum*; (2) the nature, customs and habits of the human host and his reactions to the micro-organism; and (3) the related environmental conditions.

The object of epidemiology is to determine the details of the relationships of these factors so that means may be developed to alter this relationship in favor of the human host. In syphilis this is accomplished by attempts to reduce the number of effective exposures to the *T. pallidum*. Epidemiologically this means: (1) maintenance of adequate treatment and post-treatment examination requirements among discovered infections; and (2) reduction of periods of infectiousness by early recognition of previously undiscovered infections.

Of the various methods of case-finding, contact investigation is the most direct epidemiologic approach and offers the best opportunity for discovery of early infectious cases.

In contact investigation attention is focused primarily upon the patient. The patient is the key to success. Direct questioning as to sexual intimates should follow careful explanation of the disease and adequate consideration of the patient's immediate problems, such as telling the family or interpretations to the marital partner. Names of extramarital sexual contacts are readily obtained when properly sought.

The "named" contact can be persuaded to submit to examination if the situation is adequately explained.

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Biologic False Positive Reactions in Serologic Tests for Syphilis*

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THE term "biologic false positive" is commonly used to denote those positive serologic reactions for syphilis which occur in the absence of any clinical evidence for, or history of, syphilis. The clinical recognition of such reactions is thus based on purely negative evidence derived by a process of elimination. The resolution of serologic conflicts arising from positive serologic tests in the absence of confirmatory clinical evidence has become a problem of prime importance in the diagnosis and control of the disease and has given renewed emphasis to the need for the development of serologic methods of differentiation.

Although the literature is replete with reports on serologic methods which purportedly differentiate a biologic false positive reaction, none of these empirical methods has yet been found to be valid when applied to a statistically significant number of carefully selected sera of biologic false positive and syphilitic origin. This is true of all of the methods which were recently reviewed in comprehensive discussions of the problem.¹⁻⁴ A more optimistic outlook may be justified if two newer developments in the serologic field will fulfill their initial promise. These are (1) the introduction of cardiolipin antigen and (2) the euglobulin-inhibition test. Both of these will be considered in some detail in the present paper.

CLINICAL ASPECTS OF THE PROBLEM

The general problem of biologic false positive reactions as viewed by the clinician has been so excellently discussed on numer-

ous occasions¹⁻⁷ that it does not warrant detailed consideration within the limited space of this report.* It is well established that certain diseases and febrile states are apt to elicit transitorily positive serologic tests for syphilis. These include immunizations (smallpox, typhoid, tetanus, etc.), respiratory infections (chronic and acute "common colds"), infectious mononucleosis, malaria, virus pneumonia, bacterial infections, lymphogranuloma venereum, leprosy and several others. While a positive serologic test in the presence of any one of these febrile states and diseases does not acquit the patient of the suspicion of syphilis, the chances may be even that the serologic test is of the biologic false positive type. However, biologic false positive reactions may also occur in healthy, apparently normal individuals who have no history of syphilis or of any recent disease which may have provoked a biologic false positive response to serologic tests for syphilis.^{5,7,8} In this group of individuals positive serologic tests are usually more persistent, extending over periods of months, years and sometimes persisting for life. Positive serologic tests in this group of individuals constitute the most frequent source of diagnostic errors.

Positive serologic reactions in treponemal diseases other than syphilis, such as yaws, bejel and pinta, are probably truly positive in the sense that these diseases are elicited

* A discussion of the problem has recently been given by Stokes and James (manuscript in preparation). I am indebted to Dr. John H. Stokes for the privilege of reading the manuscript prior to publication.

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by spirochetes which are morphologically and antigenically related to *Treponema pallida*. In accordance with Rein and Elsberg⁶ the term syphiloid is suggested to indicate that these positive reactions probably represent a serologic response of truly biologic origin.

Literature surveys reveal wide discrepancies in the incidence of occurrence of biologic false positive reactions in various diseases other than syphilis. While these discrepancies arise in part from variations in the number of testings and the time intervals between testings, it appears that even when frequent testing with a battery of serologic tests is employed, not all individuals afflicted with the same non-syphilitic disease will develop false positive serologic reactions.⁹ This observation together with the observation of the occurrence of (biologic false) positive serologic reactions in apparently healthy individuals has elicited the concept of "reactors," i.e., individuals who are predisposed toward the formation of circulating antibodies which are reactive toward antigens employed in serologic tests for syphilis.⁶ Any factor which stimulates the antibody-forming mechanism of the system (active and passive immunizations, infections, etc.) may thus provoke a biologic false positive reaction for syphilis. While this concept is appealing and helpful as a working hypothesis, direct experimental proof in the form of survey studies has not yet been attempted. It is the consensus among clinicians, serologists and Public Health Agencies* that a solution to the problem of biologic false positive reactions is one of the most pressing needs in the field of venereal diseases.

What then is the stumbling block which has impeded progress in the solution of this problem? It appears that every attempt that has ever been made sooner or later

meets two serious obstacles. The first of these is the lack of a base-line against which the validity of any serologic method of differentiation can be measured.

This has already been alluded to in the outset of this discussion and may be restated in more detail as follows: In order to prove that a person has a truly biologic false positive reaction, the following criteria must be fulfilled.* (1) There must be no history of infection with syphilis or gonorrhea, nor of antisyphilitic therapy. (2) The individual must have been known to be repeatedly seronegative before the first appearance of the positive reaction. (3) The first reaction must shortly have been preceded by one of the diseases or febrile states which are known to be apt to elicit a biologic false positive reaction (immunization, virus pneumonia, etc.) (4) The spinal fluid must be normal. (5) Familial and marital contacts must have been examined with no evidence for syphilis. (6) The patient must show no evidence of syphilis, especially stigmata of congenital syphilis. (7) He must become spontaneously seronegative within four to six months of the disease or episode which originally elicited the first positive reaction. While these requirements greatly limit the number of biologic false positive sera available for systematic study, the use of less strictly defined testing sera will always leave a lingering doubt as to the validity of the results. The mere fact that no evidence for syphilis has been obtained from a patient whose serum is submitted for study does not prove its absence.

However, if a serologic method of differentiation is to be developed, with testing material as carefully selected as called for by the above criteria, it must meet the following requirements³ in order to be valid: (1) Sera from syphilitic individuals with positive serologic tests should always give a syphilitic type of verification reaction. The single exception to this requirement may perhaps be in the case of individuals who are susceptible to biologic false positive reactions (reactors) and who, despite adequate therapy and complete

* An indication of this is the number of research projects which the Division of Grants and Fellowships of the National Institute of Health is sponsoring among Government, University and private laboratories, on recommendation by the Syphilis Study Section of that organization.

disappearance of all clinical manifestations of the disease, may at times become serologically positive. The distinction between resistance to therapy, serologic resistance and serologic reactor is one of the most difficult diagnostic problems in this field.

empirical use of lipoidal beef heart extract instead of specific antigens derived from human pathogenic strains of *T. pallidum*, the specificity of the serologic reaction is of high order. A similar degree of specificity of these antigens with biologic false positive

TABLE I

PROTOCOL OF EUGLOBULIN-INHIBITION TEST PERFORMED ON A TYPICAL BIOLOGIC FALSE POSITIVE SERUM*

Date	Serum No.	Fraction	Rein-Bossak Cardiolipin					V. D. R. L. Cardiolipin				
			Undil.	1:2	1:4	1:8	1:16	Undil.	1:2	1:4	1:8	1:16
4/9/48	28430	Serum	0	0	0	0	0	0	0	0	0	0
		Euglobulin	4	4	4	3	1	4	4	2	1	0
		Euglobulin + Inhibitor	0	0	0	0	0	0	0	0	0	0
5/6/48	30221	Serum	0	0	0	0	0	0	0	0	0	0
		Euglobulin	0	0	0	0	0	0	0	0	0	0
		Euglobulin + Inhibitor	0	0	0	0	0	0	0	0	0	0

* Patient R. B., History Number R-185. Clinical diagnosis: Biologic false positive; reactor due to pityriasis rosea.

(2) Sera from non-syphilitic individuals with positive serologic tests should always give the biologic false positive type of verification reaction. (3) The diagnosis of syphilis should be established in persons who consistently give the syphilitic type of verification reaction on repeated examination. (4) The diagnosis of syphilis should be excluded in persons who consistently give the biologic false positive (non-syphilitic) type of verification reaction on repeated examination.

It may be stated categorically that to date no test has been devised which fully meets these requirements. However, the introduction of cardiolipin and the development of the euglobulin-inhibition test, employed singly and in combination, have gone far toward attainment of the final goal.

The second obstacle to the solution of the present problem is of immunologic origin and relates to the nature and mechanism of the serologic reaction itself.

IMMUNOLOGIC ASPECTS

Although complement fixation and flocculation tests for syphilis are based on the

human sera can be expected only if either the reacting antibodies are immunologically identical with the antibodies to syphilis or if the two types of antibodies are immunologically cross-reactive with the same antigen. Immunological identity of the two types of antibodies would preclude any hope for any differentiation by serologic methods; whereas immunologic cross-reactivity leaves the door open by methods of selective adsorption, inhibition, etc. Alternatively, a cross-reactive factor in lipoidal antigens, if it exists, might be removed by further purification of lipoidal beef heart extracts, leaving an antigen specific for syphilis. Attempts in both directions have been recently made, with promising initial results. In the work of Neurath and co-workers, which led to development of the euglobulin-inhibition test, the serologically active antibodies were concentrated in a single serum euglobulin fraction. In the presence of a "specific" serum inhibitor, euglobulin fractions of syphilitic origin reacted with undiminished activity with beef heart antigens whereas the reaction of euglobulin fractions of biologic false positive origin with the beef heart antigen was

inhibited. In the work of Pangborn, which led to the isolation of cardiolipin (a chemically purified beef heart extract), the specificity of the antigen was markedly increased thereby eliminating many albeit not all biologic false positive reactions, without impairment of the sensitivity of the antigen toward syphilitic sera. Both of these recent advances were facilitated by reliance on basic principles of immunology and chemistry in contrast to the highly empirical "hit or miss" methods that were previously advanced. It is reassuring that after the passing of a decade since the publication of Eagle's¹⁰ comprehensive work, the serology of syphilis has found its way back to the basic concepts of immunology and chemistry.

CARDIOLIPIN ANTIGEN

Cardiolipin is a lipoidal component of beef heart extract of relatively high degree of chemical purity and reproducible chemical composition.¹¹⁻¹³ The hydrolytic cleavage products of cardiolipin are linoleic acid, oleic acid and a polyester of glycerophosphoric acid and glycerol. Its minimum molecular weight is about 740.¹⁴ Among previously known phospholipides the nearest analog is a group of plant phosphatidic acids. Like the older lipoidal beef heart extracts, cardiolipin requires cholesterol and lecithin as companion components for the performance of serologic titrations, and the preparation and standardization of purified beef heart lecithin by Pangborn¹⁵ has further increased the precision and reproducibility of cardiolipin antigen emulsions. Complement fixation and flocculation tests with cardiolipin vary in sensitivity and specificity with the relative proportions of cardiolipin, lecithin and cholesterol. Various mixture ratios have been proposed by several authors; of these, the procedures of Harris and Portnoy,¹⁶ Maltaner and Maltaner,¹⁷ Brown¹⁸ and Kolmer¹⁹ have attained prominence for complement fixation titrations, whereas the microflocculation tests proposed by Rein and Bossak,²⁰ Kline²¹

and Harris, Rosenberg and Riedel²² appear to be most recommendable. A macroflocculation test has been proposed by Kahn.²³ A review of serologic tests employing cardiolipin has been published by Rein and Coren.²⁴ While comprehensive survey studies on the relative sensitivity and specificity of cardiolipin as compared to older beef heart extracts remain to be published, preliminary data indicate clearly its high performance as regards both sensitivity and specificity. Unpublished data by Rein,* Kent* and others who have been consulted by the author indicate that cardiolipin tests are the first to become positive in syphilis and the last to disappear following therapy, and that they give higher titers than do flocculation tests with the crude lipoidal beef heart extracts. If this preliminary observation should be substantiated by general experience, the need for a battery of serologic tests would no longer exist. The use of a single, standardized antigen for both complement fixation and microflocculation tests would lessen the burden on serologic laboratories and would likewise decrease the element of doubt which so often arises in the mind of the clinician when he is confronted by contradictory serologic results obtained with several serologic technics. Caution should be observed, however, to avoid the inviting procedure of lowering the sensitivity of cardiolipin antigen emulsions for the purpose of eliminating all biologic false positive reactions which can be accomplished only at the sacrifice of lowered specificity.

In the author's laboratory the Rein-Bossak²⁰ cardiolipin microflocculation test and the V. D. R. L. slide test²² have been used hand in hand. In agreement with the experience of others no preference can as yet be given to one of these two tests over the other, except perhaps that the antigen emulsion of the V. D. R. L. test is more readily prepared in routine laboratory work and yields fewer atypical zone reactions in high titered sera.

* Private communication by Dr. Charles R. Rein and Mr. John F. Kent.

In certain diseases which show a high incidence of false positive reactions in serologic tests for syphilis, cardiolipin antigen gives considerably fewer positive reactions than do other serologic technics. In sporozoite-induced human malaria Rein and Kent⁹ found that the highest percentage of positive reaction was observed with the Kahn standard test, whereas the Rein-Bossak cardiolipin microflocculation test was weakly positive in only three of fifty-seven sera which were positive to one or the other of the older tests. A similarly high degree of specificity was obtained in a separate study by Kline as quoted by Rein and Kent.⁹

While a like specificity of cardiolipin antigen probably exists in other diseases which elicit biologic false positive reactions, this is not true of all of them. Little difference has been observed between cardiolipin tests and some of the older tests in biologic false positive reactions due to leprosy,²⁴ and preliminary data suggest that in infectious mononucleosis^{24,25} cardiolipin may possibly be even less reliable in serologic tests for syphilis than tests employing cruder beef heart extracts. No distinction between these two types of tests could be made when they were applied to a study of sera from patients with syphiloid diseases.²⁴

While the introduction of cardiolipin in serologic tests for syphilis marks definite progress toward at least two generally accepted aims, i.e., the standardization and reproducibility of antigen preparations and increased sensitivity and specificity for the serologic diagnosis of syphilis, the third aim, namely, elimination of biologic false positive reactions, has not been achieved by cardiolipin.

EUGLOBULIN-INHIBITION TEST

It would take us far afield to consider here in detail the fundamental aspects of the work which led to the development of this technic. Reference is made to a series of publications which appeared in 1947^{4,26-29} and to the publication of the results of a

cooperative survey study which is to be published in the near future and which will also describe the technic as used at the present time. A brief résumé of the nature of this technic follows:

The Serologically Active Euglobulin Fraction. In common with other immunologically active antibodies, the antibodies in syphilis as well as the antibodies which give rise to biologic false positive reactions for syphilis are not evenly distributed among all serum protein components, but are limited to that globulin fraction which is commonly denoted as *gamma* globulins, of which only a minutely small fraction, however, is serologically active. Concentration of the antibodies can be achieved by so-called iso-electric precipitation. This involves ten-fold dilution of the whole serum with concomitant lowering of the pH of the diluted serum to 6.2 to 6.4. The fraction which precipitates is readily soluble in phosphate buffer, pH 6.8, and the reacting antibodies can be concentrated (and their serologic titer per unit volume increased) by dissolving the precipitate obtained from a relatively large volume of serum (5.2 cc. or more) in a relatively small volume of buffer (1 cc. or less). This euglobulin fraction, representing about 7 per cent of the total proteins, is composed of about 50 per cent *gamma* globulin, about 20 per cent each *beta* globulin and *alpha*₂ globulin, no *alpha*₁ globulin and only traces of serum albumin. About 13 per cent of the total serum *gamma* globulins are precipitated in the euglobulin fraction but this fraction contains 50 per cent or more of the total serologically active antibodies, indicating a preferential concentration of the antibodies relative to the total *gamma* globulins in this fraction. This euglobulin solution is used for quantitative serologic titrations, using buffer as diluent. The titer thus obtained is used as a basis of reference to judge the degree of inhibition (*vide infra*).

The Inhibitor. This is a human serum protein fraction which is serologically inactive and which was originally believed to be associated with human serum albu-

min.³⁰ Further studies have shown that the inhibitory factor is part of the lipid-rich α_1 globulin fraction which precipitates as Fraction IV-1, a by-product of the plasma fractionation process which has been developed for the large scale preparation of serum albumin.³¹ The inhibitory factor is found in good yields in about 70 per cent of all human sera that have been tested, normal and syphilitic as well as sera from patients who developed biologic false positive reactions for syphilis. This factor is conspicuously absent in sera from patients with liver disease. Recent work by Volkin³² in the author's laboratory has shown that the lipoidal component of the inhibitory protein fraction has all the properties of serum lecithin. Egg lecithin, however, does not possess specific inhibitory properties, nor do the α_1 globulin fractions from sera of species other than man.

Laboratory Performance of the Euglobulin-Inhibition Test. The essential steps in the performance of this test are as follows: (1) The solution of the euglobulin fraction, twice as concentrated as this fraction occurs in the whole serum, is subjected to quantitative serologic titrations in serial two-fold dilutions with buffer as diluent. This yields the control titer in units (calculations of units of titer as described previously⁴). (2) Another aliquot of the euglobulin solution to which a specified amount of inhibitor has been added is similarly subjected to quantitative serologic titrations in serial two-fold dilutions, using the inhibitor solution as diluent (in order to maintain a constant inhibitor concentration in each dilution). The degree of serologic positivity in each dilution in the presence of the inhibitor is compared with the degree of positivity of the corresponding dilution of the euglobulin control solution.

Complete inhibition by the inhibitor (solution b) is indicative of a *biologic type of reaction*. Conversely, failure of inhibition is indicative of the *syphilitic type of reaction*.*

* Since in the presence of a large excess of antibodies (high-titered fractions) the capacity of the inhibitor may be exceeded, yielding incomplete inhibition, a quantitative

If the euglobulin solution is serologically negative, the euglobulin-inhibition test is, of course, not applicable even if some serologic activity is demonstrable in the whole serum. In that case the reaction is said to be of the *negative type*.

Experience has shown that the euglobulin-inhibition test is more specific when used in conjunction with cardiolipin antigens than with antigens containing crude beef heart extracts (Mazzini, Kline, Kahn). As a result of this experience, the euglobulin-inhibition test is now being used exclusively in conjunction with the Rein-Bossak²⁰ and the V. D. R. L.²² antigens.

Validity of the Test. In a preliminary survey analysis²⁹ it was found that about 95 per cent of all sera from patients with syphilis, regardless of stage of disease, serum titer and previous antisyphilitic therapy, gave the syphilitic type of reaction. The single exception was the group of low-titered sera from untreated patients with early primary syphilis in which the agreement between diagnostic status of the patient and the type of serologic reaction was hardly better than chance.* In the same survey it was found that in about 95 per cent of all serologically positive sera from patients without syphilis, as judged for the most part by the criteria set forth earlier in this paper, the biologic false positive type of reaction was obtained. Here, too, the type of serologic reaction was independent of serum titer and independent of the disease or febrile condition which appeared to have elicited a positive serologic test.

More recently, a cooperative survey study has been initiated by the Syphilis Study Section of the United States Public Health Service, with four participating laboratories (including that of the author), to test the validity of the euglobulin-in-

hibitory scale has been recently introduced to resolve reactions in which incomplete inhibition occurs.

* Two alternative explanations for the failure of this test in this group of sera have been suggested.²⁹ Resolution of these discrepancies is obtained as soon as the serum titer increases, whereupon the syphilitic type of reaction makes its appearance. In all other instances the euglobulin-inhibition test is independent of serum titer.

hibition test when performed in laboratories other than that of the originator.* The serologic techniques of the four laboratories were standardized and identical reagent preparations and serum specimens were used. Only sera from patients with unequivocally determined clinical status were included in the evaluation of the results but without consideration of serum titer. Comparison between serologic results and clinical status was made after the serologic testing had been completed in each of the four laboratories. A final evaluation of the results will be published in the near future under joint authorship by the representatives of the four laboratories. Tentative statements made herein represent only the opinion of the author of this report.

The sera from patients believed to have biologic false positive reactions for syphilis were for the most part from patients with sporozoite-induced malaria (about 75 per cent). About 93 per cent of the positive serologic reactions observed in the entire group of biologic false positive sera were of the biologic type and about 5 per cent were of the syphilitic type. About 95 per cent of all positive sera from patients with syphilis gave the syphilitic type of reaction in contrast to only 1 per cent which gave the biologic false positive type of reaction. While this agreement between clinical status and serologic type of reaction is encouraging, it should not distract from apparent limitations and discrepancies that were evident. Thus, variable results were sometimes obtained on the same specimen in different laboratories. Discrepancies were sometimes also noted when the results obtained on the same specimen with two different antigen emulsions (Rein-Bossak and V. D. R. L.) were compared with each other. It is obvious that these and similar

sources of error and inconsistency will have to be traced and eliminated before this test can be submitted for general use. Also, the inhibitory fraction now in use is far from pure, containing about 98 per cent of inactive protein and lipid components. Work on further purification is in progress.³²

Comments Regarding the Test. There is no assurance as yet that even under optimum experimental conditions the euglobulin-inhibition test will completely resolve serologic conflicts in the diagnosis of syphilis. It may well be that there exist inherent factors in this test which limit its resolving power, and that other concepts and approaches may be found to penetrate the problem more deeply. Alternatively, it would not be surprising to find barriers of biologic origin which will always prevent us from reaching the degree of perfection which is required for complete resolution of the problem. It would take us into the realm of speculation if we were to dwell on the biologic and immunologic aspects of the nature of biologic false positive reactions. But the question may be raised whether we are justified in assuming immunologic identity of all antibodies which give rise to conditions of positive serologic tests in the absence of syphilis. Perhaps some of these "non-specific" antibodies are too closely related to the antibodies to syphilis to enable us ever to differentiate them from the syphilitic antibodies by any serologic technic. To retrace our steps even further, what is the threshold between positive and negative serologic tests? How "negative" is a negative test for syphilis or, conversely, what minimal antibody concentration is required before they elicit a positive reaction with lipoidal antigens? Lastly, what is the relation of serologic tests to subclinical manifestations of the disease?

• An illustration of the problem of absolute *versus* relative serologic negativity is furnished by repeated observations with the euglobulin-inhibition test which show that a serum euglobulin fraction may be strongly positive, whereas whole serum may be negative or at best give a "doubtful" reaction. Such

* This survey study has been carried out under the sponsorship of the Syphilis Study Section of the Division of Grants and Fellowship, National Institute of Health, and includes in addition to the author's laboratory: The Venereal Disease Research Laboratory, Staten Island; The Division of Serology, Army Medical School, Washington, D. C.; and the Laboratory of Dr. C. R. Rein, New York. A joint report will be published by the senior investigators of these laboratories.

an increase in reactivity has been observed even with cardiolipin antigens, as tabulated for a representative case in Table 1. It is more often seen in sera from patients who give biologic false positive reactions than in syphilitic sera but occurs only rarely in sera from normal individuals. The reason for the increased reactivity is two-fold: (1) Concentration of the antibodies in the more concentrated euglobulin fraction, as compared to the whole serum; (2) elimination from the euglobulin fraction of the inhibitory factor which occurs in the α_1 globulin of the whole serum. Survey studies of the serologic activity of euglobulin fractions of sera from normal individuals, from individuals with recent episodes of diseases which tend to elicit biologic false positive reactions and from fully treated syphilitic patients should shed light on the problem of absolute and relative serologic negativity.

CONCLUSIONS

In conclusion we may state that serologic analysis has not yet reached the stage where it will take the place of clinical examination and probably never will. However, two recent developments in the field of serologic tests for syphilis have provided us with promising tools to aid the clinician in the diagnosis of syphilis. One of these, i.e., the introduction of cardiolipin, has increased the sensitivity and specificity of the serologic reaction in sera from patients with syphilis and has lessened the incidence of biologic false positive reactions in malaria and possibly in other diseases. The other development is the euglobulin-inhibition test which has been shown to distinguish biologic false positive reactions in more than 90 per cent of sera from carefully selected individuals who according to the best clinical judgment have never had syphilis, and to recognize syphilis in over 95 per cent of all sera from patients who are known to have the disease (except low-titered sera from untreated patients with early primary syphilis). It remains to be seen whether an equal resolution can be

obtained with this method if the other two requirements previously stated are put to test: The diagnosis of syphilis should be established in persons who consistently give the syphilitic type of reaction on repeated examination; the diagnosis of syphilis should be excluded in persons who give the biologic false positive (non-syphilitic) type of reaction on repeated examination.

SUMMARY

The problem of biologic false positive reactions in serologic tests for syphilis has been considered in relation to certain basic clinical and immunologic aspects. These include the clinical definition and recognition of a biologic false positive reaction, the requirements of a valid serologic method of differentiation and the immunologic nature of the antibodies and antigens. Recent developments in the serologic diagnosis of syphilis are reviewed and critically considered, with special reference to the introduction of cardiolipin and the euglobulin-inhibition test. The present status of the problem of biologic false positive reactions has been evaluated, with consideration of the possible clinical and immunologic limitations to complete resolution of the problem.

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Nationwide Results in the Treatment of Early Syphilis with Penicillin*

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FIVE years have elapsed since Mahoney, Arnold and Harris¹ made the first preliminary report on the activity of penicillin in syphilis. It now becomes possible to speak in terms of "five-year cures" following the use of penicillin since three of the original four patients have remained symptom-free and seronegative for that length of time following their initial course of therapy.² There is reason to believe on the basis of earlier experience with metal chemotherapy³ that this is suggestive evidence that "cure" actually has been effected as a direct result of the new therapeutic procedure.

Factual data on penicillin in the treatment of early syphilis have been amassed with great rapidity. This has been possible because there have been in progress in this country two cooperative nationwide studies, one begun under the auspices of the Committee on Medical Research and subsequently continued by the Syphilis Study Section, National Institutes of Health, and the other under the direction of the Venereal Disease Division, United States Public Health Service, through its Rapid Treatment Centers. It is with the results obtained in these two studies^{4,5} that the present report is concerned and upon which it is mainly based.

From time to time it is desirable to remind ourselves that the ultimate goal is to find the *ideal* treatment for syphilis. In an earlier paper⁶ the ideal treatment for syphilis was defined as one that is (1) completely and uniformly effective, (2) entirely devoid of toxicity and (3) readily administered with

a minimum of inconvenience to the patient and to his physician. In this paper treatment with penicillin was compared with previously available methods of therapy and the following tentative evaluation made: "Penicillin is effective, but not always completely so. It is, in marked contrast to metal chemotherapy, non-toxic, approaching the ideal in this respect. It is relatively easy to administer, and therapeutically effective amounts can be given in a comparatively brief period of time." These statements are as true now as they were two years ago.

As data continue to be accumulated additional conclusions can be drawn although these still are to be considered as tentative because of the notorious chronicity of syphilitic infections. For convenience the more recent advances in the penicillin therapy of syphilis will be discussed in terms of the three attributes of the hypothetical "ideal" form of treatment for this disease.

EASE OF ADMINISTRATION

The earliest schedules of penicillin therapy in early syphilis were those utilizing aqueous solutions of amorphous penicillin given at intervals of two, three or six hours. Such schedules had the distinct disadvantage of necessitating hospitalization because of the rapid excretion of penicillin when administered in aqueous solution.

In order to make ambulatory treatment schedules feasible, a modified penicillin with prolonged activity is required. Many attempts have been made to extend the

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duration of penicillin action, either by delaying its absorption or by blocking its renal excretion. The first satisfactory preparation, penicillin in oil with 4.8 per cent beeswax (P.O.B.),⁷ has been evaluated in both of the nationwide studies and found to be at least as efficacious as comparable amounts of penicillin in aqueous solution. Superior to P.O.B. in several respects is the more recently developed procaine penicillin, a crystalline preparation which is relatively insoluble in tissue fluids and which results in serum concentrations of longer duration than are obtained with P.O.B. The procaine preparation has the additional advantage of not causing painful local reactions and thus of making the course of therapy more tolerable to the patient.

A suspension of crystalline procaine penicillin G in oil with 2 per cent aluminum monostearate⁸ is currently being evaluated by the clinics cooperating with the Syphilis Study Section. With this preparation it is possible to maintain detectable (and in syphilis, presumably effective) serum concentrations of penicillin for approximately seven days following a single intramuscular injection of 1.2 million units (4 cc.).

TOXICITY

The fact that penicillin even after five years of extensive use has caused no reported fatalities and comparatively few serious reactions continues to be one of the most remarkable attributes of the drug.

The most frequently encountered untoward reaction is allergic dermatitis—most often urticaria or erythrodermia, the latter occasionally followed by exfoliation.⁹ There is evidence that crystalline penicillin G is somewhat less allergenic in this respect than were the earlier and less pure penicillin preparations. Tending to counterbalance this is the fact that as more and more patients have been subjected to repeated courses of penicillin, the incidence of allergic reactions has increased. There is some indication, however, that dermal sensitization is less common following the

use of procaine penicillin than with older preparations.¹⁰

Jarisch-Herxheimer reactions are frequent during penicillin therapy for early syphilis, with fever and transitory intensification of the tissue reaction occurring in approximately one-half of the patients treated.¹¹ The Milian type of reaction ("erythema of the ninth day") has not been reported although the delayed and dark-field-negative "exacerbation of secondary lesions" described by Thomas, Landy and Cooper¹² has much in common with the Milian phenomenon. Delayed "serum-sickness-like" reactions occur but are not frequent.¹³

THERAPEUTIC EFFICACY

The greatest single drawback to the use of penicillin in the treatment of early syphilis continues to be the comparative frequency with which recurrent infectious lesions are reported. As a result of the cooperative studies, the following facts now seem to be apparent:

1. Penicillin alone (at least with any of the schedules and time-dose relationships thus far evaluated) is somewhat inferior in therapeutic activity to properly administered metal chemotherapy, provided the latter is completely carried out.

It is easy to overlook the fact that metal chemotherapy, despite its toxicity and the difficulties in case-holding inherent in its proper administration, is highly effective. With arsenicals and bismuth employed in such time-dose relationships as the Army's intensive courses compressed into periods of twenty-six weeks¹⁴ or of twenty days,¹⁵ the incidence of treatment failures was 4.6 and 4.3 per cent, respectively. With amorphous penicillin in aqueous solution (2.4 million units, in divided doses given every three hours over a period of seven and one-half days) administered to a comparable group of (Army) patients who were followed for approximately the same length of time, the failure rate was 10.6 per cent.¹⁶

2. Crystalline penicillin G is superior to amorphous penicillin especially when the

latter contains a significant content of penicillin K.

The results of penicillin therapy in early syphilis are complicated by the fact that the first studies were carried out with amorphous penicillin of unknown composition.¹⁷ As the several penicillin species were recognized, information became available from a group of cooperating laboratories indicating that penicillin G is more efficacious against *Treponema pallidum* than any of the other known species.¹⁸ Of particular significance is the relatively low therapeutic activity *in vivo* of penicillin K.¹⁹ With the development of crystalline penicillin G, this latter product was studied exclusively and the clinical data, now of statistical validity, confirm its superiority over the crude penicillin preparations used in the earlier studies. (Fig. 1.)

3. The therapeutic results with penicillin-oil-beeswax (P.O.B.) have been at least as good as, and perhaps slightly better than those with comparable amounts of penicillin in aqueous solution.

The study of ambulatory schedules of penicillin in various absorption-delaying vehicles is being carried on in nine cooperating clinics* and supported by generous contributions of penicillin from ten pharmaceutical firms.†

The first product to be evaluated was penicillin-oil-beeswax (P.O.B.). A recent analysis^{4b} of the results of therapy on an ambulatory basis indicates that this preparation is at least as active as penicillin in aqueous solution and perhaps slightly more so. (Fig. 2.)

4. The results of penicillin therapy in early syphilis are influenced to a significant degree by the composition of the patient

population treated (especially race, sex and stage of disease distributions).

The proper interpretation of statistical data regarding the use of penicillin in early syphilis requires that the composition of the clinic population treated be analyzed

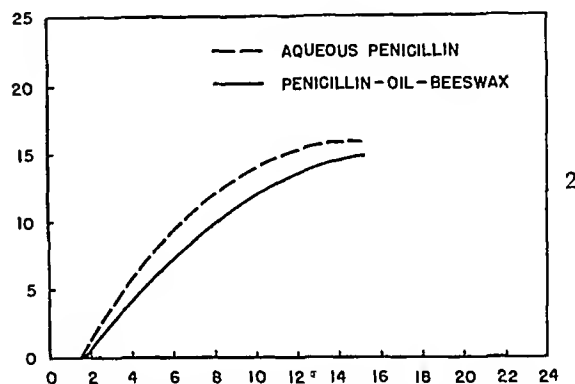
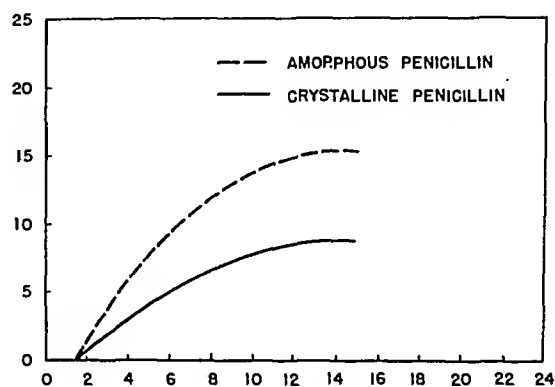


FIG. 1. Cumulative total failure rates following therapy for early syphilis (4.8 million units in seven and one-half days). Comparison of amorphous penicillin with crystalline penicillin G. (Syphilis Study Section data.)

FIG. 2. Cumulative total failure rates following therapy for early syphilis (4.8 million units in seven and one-half days). Comparison of aqueous penicillin with penicillin-oil-beeswax. (Syphilis Study Section data.) (The numbers along the ordinate in both illustrations represent cumulative percentage failing; those along the abscissa represent the months following treatment.)

* Bellevue Hospital (E. W. Thomas), Columbia University (E. G. Clark), Emory University (A. Heyman), Johns Hopkins University (J. E. Moore), Medical College of Alabama (R. O. Noojin), Southwestern Medical Foundation (A. G. Schoch), University of Pennsylvania (J. H. Stokes), University of Virginia (D. C. Smith), Vanderbilt University (R. H. Kampmeier).

† Abbott Research Laboratories, Bristol Laboratories, Commercial Solvents Corporation, Heyden Chemical Corporation, Lederle Laboratories, Lilly Research Laboratories, Charles Pfizer & Company, Schenley Laboratories, Squibb Institute for Medical Research, Upjohn Company.

with respect to race, sex and (probably most important of all) stage of disease distribution.

For some time it was a matter of considerable concern to syphilologists that there were significant discrepancies between the results obtained in different clinics utilizing comparable schedules of penicillin therapy. The results reported by Arnold and his co-workers²⁰ at the Venereal Disease Research

Laboratories (VDRL), U.S. Marine Hospital, Staten Island, for example, have been consistently superior to those from other clinics cooperating in the nationwide studies. When the data of different groups of investigators are analyzed²¹ with respect to

the patient population (Table 1), it becomes apparent that the results of penicillin therapy must be interpreted in consideration of several factors in addition to the treatment schedule employed. As one illustration, it can readily be demonstrated that

TABLE 1
CLINIC POPULATIONS (RACE, SEX AND STAGE OF DISEASE DISTRIBUTIONS) IN TWO SERIES OF PATIENTS WITH EARLY SYPHILIS⁷

Venereal Disease Research Laboratories (728 Patients) ²⁰							
Male				Female			
White		Negro		White		Negro	
Primary	Secondary	Primary	Secondary	Primary	Secondary	Primary	Secondary
53.7%	22.8%	11.4%	8.6%	1.2%	1.5%	3%	.5%
76.5%		20.0%		2.7%		0.8%	

Central Statistical Unit (566 Patients) ²¹							
Male				Female			
White		Negro		White		Negro	
Primary	Secondary	Primary	Secondary	Primary	Secondary	Primary	Secondary
10.8%	7.4%	14.7%	14.3%	4.3%	10.0%	7.9%	30.6%
18.2%		29.0%		14.3%		38.5%	

	Per Cent		Per Cent
Male.....	96.5	Female.....	3.5
White.....	79.2	Negro.....	20.8
Primary.....	66.7	Secondary.....	33.3

	Per Cent		Per Cent
Male.....	47.2	Female.....	52.8
White.....	32.5	Negro.....	67.5
Primary.....	37.7	Secondary.....	62.3

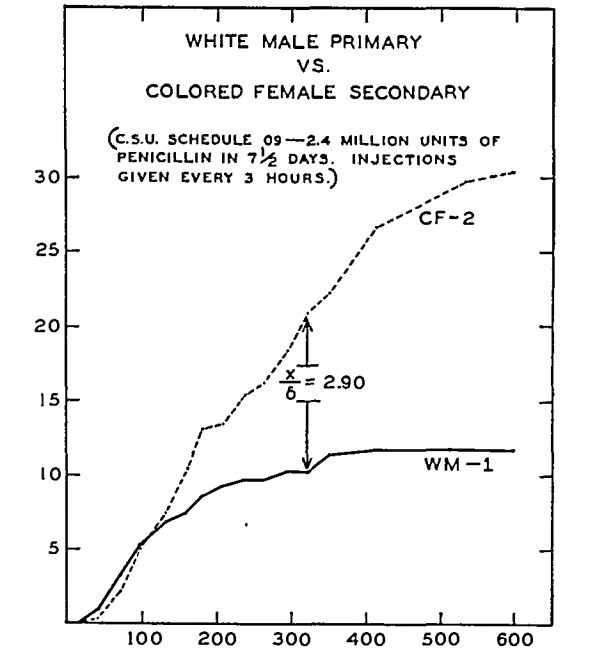


FIG. 3. Cumulative total failure rates following penicillin therapy. Comparison of Negro females with secondary syphilis and white males with primary syphilis.⁷ (The numbers along the ordinate represent cumulative failure rate; those along the abscissa represent days after treatment.)

the treatment of white male patients with primary syphilis is far more satisfactory than is the treatment of negro female patients with secondary syphilis. (Fig. 3.)

5. The results of penicillin therapy are somewhat better than the available data indicate because of the considerable number of reinfections that have been included as treatment "failures."

At the inception of the penicillin study, it was decided to include as treatment "failures" all patients with recurrent, infectious, mucocutaneous lesions. This decision was made in the knowledge that a certain number of reinfections would be included but it was dictated by the practical difficulties involved in the differentiation of reinfection from relapse. During the past few years more and more evidence has accumulated that reinfections are frequent following adequate therapy administered early in the course of an original infection with syphilis²² although there still is no unanimity of opinion as to precisely how

differentiation from relapse can be established indubitably.²³

Accepting the probability that the cooperative clinical data include as "failures" an unknown and perhaps not inconsiderable number of reinfections (which imply treat-

ment²³ indicates that even massive intravenous penicillin therapy is entirely inadequate if given over short periods.

The results of the cooperative studies indicate no significant improvement in the failure rates when the amount of aqueous

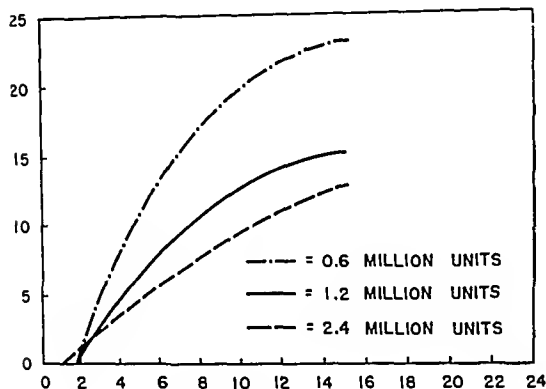


FIG. 4.

FIG. 4. Cumulative clinical failure rates following therapy for secondary syphilis in males. Comparison of three schedules varying in total dosage of penicillin. (Syphilis Study Section data.)

FIG. 5. Cumulative total failure rates following penicillin therapy for early syphilis (1.2 million units in seven and one-half days). Comparison of two schedules varying in time interval between injections. (Syphilis Study Section data.) (The numbers along the ordinate in both illustrations represent cumulative percentage failing; those along the abscissa represent the months following treatment.)

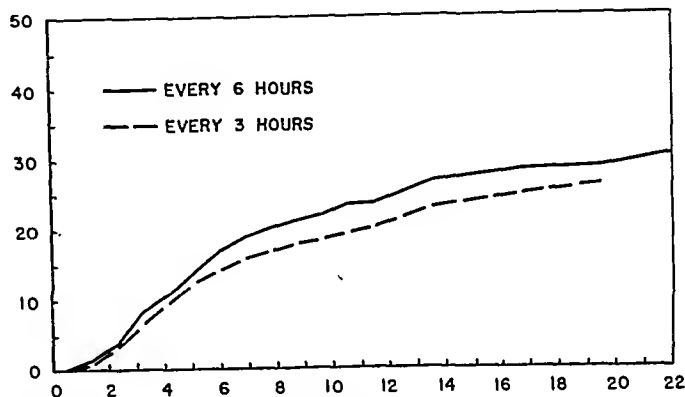


FIG. 5.

ment success rather than failure), the results are to be interpreted as being more favorable than is indicated but in a proportion that thus far cannot be delineated.

CAN THE THERAPEUTIC ACTIVITY OF PENICILLIN BE ENHANCED?

In consideration of the fact that penicillin falls short of the ideal form of therapy largely on the basis of its limitations in therapeutic efficacy, it is pertinent to inquire whether and by what means the activity of penicillin can be enhanced. Several possibilities currently exist:

1. Alter the time-dose relationships of penicillin administration by giving sufficient penicillin to increase further blood and tissue concentrations. *T. pallidum* is an organism extremely susceptible to the action of penicillin.²⁴ Although the tissue concentrations maximally effective for its destruction *in vivo* have not been determined, it is probable that relatively low concentrations suffice provided they are available at the site of action for a sufficiently long period of time. The experience of Peters and Bar-

penicillin per injection is increased from 20,000 to 40,000 to 80,000 units. Moreover when the total amount of penicillin is increased from 2.4 to 4.8 or 9.6 millions of units, no striking decrease in the failure rate occurs. Schedules involving less than 2.4 million units have resulted in progressively higher percentages of failure. (Fig. 4.)

The time intervals between injections of penicillin can also be altered. The only effect of shortening the interval between injections of penicillin is to increase serum and tissue concentrations of the drug or, in the event that injections are widely spaced, of shortening the interval during which inadequate concentrations are present at the site of action.

Were it essential that maximally effective penicillin concentrations be maintained constantly at the site of action, it would seem reasonable to expect better results with such absorption-delaying preparations as penicillin-oil-beeswax. Actually, it appears not to be essential that penicillin levels be maintained constantly, provided the "penicillin-free" interval is short enough to

prevent renewed multiplication of microorganisms.²⁶

There is no indication from the cooperative clinical data that injections of aqueous penicillin given every two hours are superior to comparable amounts of the drug ad-

Even were it possible significantly to increase the therapeutic effectiveness of penicillin by prolonging over a period of months the total duration of the course of antisyphilitic treatment, such a procedure inevitably would increase the difficulties in

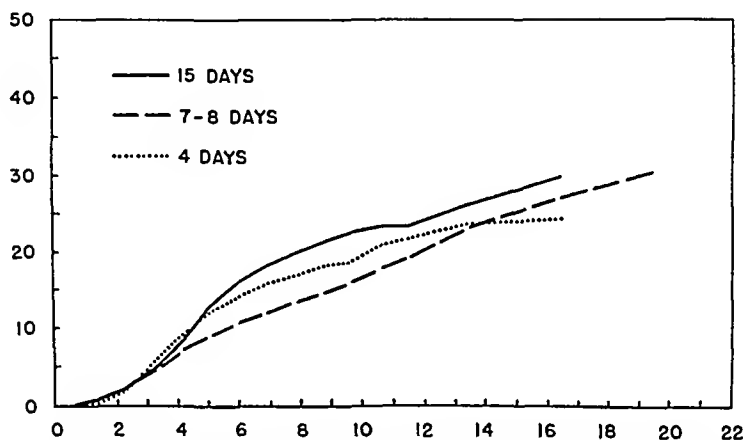


FIG. 6. Cumulative total failure rates following penicillin therapy for early syphilis (2.4 million units, injections every three hours). Comparison of three schedules varying in time interval between injections. (Syphilis Study Section data.) The numbers along the ordinate represent cumulative percentage failing; those along the abscissa represent the months following treatment.)

ministered every three hours. Moreover, schedules involving injections at intervals of six hours have proved to be as effective as those calling for injections every three hours. (Fig. 5.)

The total duration of penicillin therapy could be prolonged. Eagle²⁷ maintains that "the therapeutic activity of a given dosage of penicillin rests in large part, if not primarily, on the total length of time for which it remains at bactericidal levels, with particular emphasis on the time for which it is present at the maximally effective concentration, plus the time required for the organisms to recover from the drug and effectively resume multiplication."

Unfortunately, the cooperative clinical data are insufficient either to support or categorically to negate this contention since only a few patients have been treated with prolonged courses of therapy. Within the limited duration of therapy range of from four to seven and one-half to sixteen days, cumulative failure rates have been almost identical. (Fig. 6.)

case-holding and make such schedules impracticable in mass application.

2. Administer other spirocheticides concomitantly with penicillin, e.g., metal chemotherapy. Following the laboratory demonstration of a synergistic action between penicillin and arsenoxide²⁸ and of a similar effect when penicillin and bismuth are used in combination,²⁹ there were numerous attempts to formulate combined schedules that might be feasible for routine clinical practice.

The results thus far suggest that although schedules utilizing penicillin and arsenicals and bismuth have given somewhat lower failure rates than those with penicillin alone (Table II), the advantage gained is at the expense of increased risk to the patient. Whenever the schedule of therapy includes arsenoxide for use concomitantly with penicillin, the incidence of serious reactions is increased and occasional treatment death results, most often from hemorrhagic encephalitis. (Table III.)

The Army³⁰ and the Navy³¹ both currently advise against the use of metal chemotherapy as part of the first course of treatment and suggest that arsenoxide and bismuth be reserved for relapsing cases. The Veterans Administration has discarded

administer but which has certain limitations in therapeutic activity (at least as it has thus far been employed). The outlook for practical methods to enhance the efficacy of penicillin by altering the time-dose relationships of its administration or by the

TABLE II
COMPARISON OF PENICILLIN ALONE VERSUS PENICILLIN PLUS METAL CHEMOTHERAPY—RESULTS OF THERAPY TWELVE TO FIFTEEN MONTHS FOLLOWING TREATMENT FOR SECONDARY SYPHILIS (RAPID TREATMENT CENTERS DATA)

Schedule of Therapy					Total Cases Observed for 12 to 15 Mo.	Cumulative Per Cent Re-treated
Penicillin			Metal Chemotherapy			
Amount (Million Units)	Interval (Hr.)	Duration (Days)	Arsen-oxide (Injections)	Bismuth (Injections)		
1.2	3	7½	..	.	135	25.4
1.2	6	7½	.	.	326	23.2
1.2	3	4	.	.	148	22.4
1.2	3	7½	8	..	462	16.9
1.2	3	9	5	..	310	15.6
1.2	3	9	5	3	1237	14.5

metal chemotherapy altogether and recommends a second course of penicillin for patients who have evidence of relapsing early syphilis.³²

Eagle and Fleischman^{33,34} recently have demonstrated that although in itself bacitracin is only moderately active in syphilis, this substance in combination with penicillin exerts a striking degree of synergistic effectiveness in terms of the amount of each drug required to effect cure of the experimental infection. In the hope that the combination may increase the percentage of patients cured with relatively innocuous and readily administered therapeutic agents, a preliminary clinical trial of these antibiotic substances has been organized.

SUMMARY

In penicillin there is added to the armamentarium of the syphilotherapist a drug of practically negligible toxicity which is becoming more and more convenient to

TABLE III
SEVERE REACTIONS AND DEATHS REPORTED BY THIRTY-SIX RAPID TREATMENT CENTERS FROM JULY 1946 THROUGH NOVEMBER 1947

Type of Treatment	Total Patients Treated	Severe Reactions		Treatment Deaths	
		No.	Rate per 1,000	No.	Rate per 1,000
Penicillin alone.....	43,734	240	5.1	0	0
Penicillin with arsenoxide.....	118,544	1632	13.8	16	0.14

concomitant use of other spirocheticidal substances is discussed.

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Penicillin Treatment of Early Syphilis*

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DURING the past five years a great many facts have been collected about the treatment of early syphilis with penicillin but we have not yet learned with certainty the optimum schedules of therapy. Most of the data now available were compiled during the late war and the first two years after the war when the reservoir of infectious syphilis was at its peak. The high incidence of early syphilis during these years afforded a great mass of material for study but the evaluation of the results of therapy was greatly handicapped by an undetermined percentage of reinfections which are more prone to occur when the reservoir of infectious syphilis is high than when it is low. Of even more consequence, clinical research in the treatment of syphilis with penicillin has been unable to keep pace with the changes that have occurred in penicillin preparations. Obviously the time-dose relationship of penicillin treatment schedules is dependent on the rate of absorption of the penicillin preparations used.

The data on the results of the treatment of early syphilis with penicillin now available are limited to the use of aqueous solutions and penicillin in oil and beeswax (POB). As is well known, aqueous solutions of penicillin are rapidly absorbed and rapidly excreted. Injections of 20,000 to 50,000 units of penicillin in water or saline must be given every two to four hours to obtain fairly continuous blood concentrations of the antibiotic, and injections of 300,000 to 600,000 units of POB must be given daily to obtain continuous blood concentrations.

SIGNIFICANCE OF BLOOD CONCENTRATIONS OF PENICILLIN

The determination of blood concentrations of penicillin has little significance in the treatment of syphilis but it has great value in informing us of the rate at which penicillin is absorbed. High peaks of penicillin in the blood are apparently no more effective in destroying the *Treponema pallidum* than very low blood concentrations. As a matter of fact many cases of early syphilis have been cured with doses of penicillin that gave little or no demonstrable blood concentrations. The duration of penicillin treatment of syphilis is even more important than the dosage. The rate at which penicillin preparations are absorbed determines the frequency with which individual injections must be given. Eagle and his co-workers¹ proved that early syphilis in rabbits can be cured in a single day by giving about 200 times the total dose of penicillin in aqueous solution that is required to cure rabbits in four days. But the important factor in this observation is the prolonged action of such large doses rather than the high concentration of penicillin in the blood. From the information we now have, penicillin must be active within the body for two to four days to cure many cases of early syphilis and the *optimum period of treatment seems to be at least fifteen days*.

VALUE OF SLOWLY ABSORBED PREPARATIONS

The best results of penicillin therapy of early syphilis so far have been obtained

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with from 300,000 to 600,000 units of POB injected daily over a fifteen-day period. Following a single injection of 300,000 units of POB blood concentrations of penicillin have been found for twenty to thirty hours. Preparations of penicillin that are absorbed slowly for forty-eight or more hours after a single injection need not be given daily. Within the past year it has been found that the addition of aluminum monostearate (a water repellent substance) to mixtures of insoluble salts of penicillin and oil greatly delays the absorption of the penicillin. A single injection of 300,000 units of procaine penicillin G in oil gelled with 2 per cent aluminum monostearate has given demonstrable blood concentrations of penicillin for at least four days in over 90 per cent of several hundred cases.² Single injections of 1.2 million to 2.4 million units of this preparation have given demonstrable blood levels of penicillin for at least five days and in some cases for seven days. Thus, the way is now open for greatly modified schedules of treatment for early syphilis. A single treatment with 2.4 million units of procaine penicillin G in oil and 2 per cent aluminum monostearate should be equivalent to injections of 50,000 units in aqueous solution every three hours for five or six days. An injection of 1.2 to 2 million units of procaine penicillin in oil and aluminum monostearate at weekly intervals for only two weeks should be equivalent to daily injections of 300,000 units of POB for fifteen days. Therefore, it may well be that early syphilis can now be cured with no more than one injection of slowly absorbed penicillin or at most with one injection a week for two weeks.

In view of such developments the data on past schedules of penicillin therapy of early syphilis are of value chiefly as a background for determining the optimum total dosage of penicillin and the optimum time of treatment.

DATA NOW AVAILABLE

Extensive and carefully controlled studies of a variety of penicillin treatment schedules

for early syphilis have been conducted during the past five years under the direction of a Subcommittee for Venereal Diseases originally sponsored by the National Research Council and later by the National Institute of Health. In addition, much information has been compiled by the Venereal Disease Division of the United States Public Health Service. Data are still in the process of being collected and evaluated by these agencies. The evaluation of anti-syphilitic therapy is a slow process and it is still impossible to state with certainty the optimum time during which early syphilis should be treated. At present the greatest amount of information has been compiled for treatment schedules of four to eight days. More recent experience with fifteen-day schedules of treatment indicates that the longer period of therapy has given better results but further time must elapse before definite statements can be made to this effect.

TREATMENT OF EARLY SYPHILIS WITH AQUEOUS SOLUTIONS OF PENICILLIN

The use of aqueous solutions of penicillin for the treatment of early syphilis requires hospitalizing the patient. As a result most of the treatment schedules with this preparation have been confined to a period of from four to seven and one-half days. A variety of time-dose relationships has been studied and penicillin has been used in association with arsenical drugs and bismuth. The total dose of penicillin has varied from 600,000 to 5,000,000 units and the interval between individual injections has varied from two to six hours.

At Bellevue Hospital we have treated large series of patients with early syphilis using eight different schedules of therapy with aqueous solutions of penicillin alone or penicillin combined with arsenicals. Elaborate tables showing the cumulative failure rates with each schedule of therapy for the various stages of early syphilis, including relapses and reinfections, have been prepared but they are not included in this

report because of the limitation of space and the fact that they, as well as reports from the Central Statistical Unit and the United States Public Health Service, can be briefly summarized satisfactorily without going into great detail.

From the data now available the following conclusions regarding the rapid treatment of early syphilis with aqueous solutions of penicillin and other antisypilitic agents can be made:

1. When individual injections of aqueous solutions of sodium penicillin were given every two to four hours for a period of seven and one-half days, a total dose of 2.4 million units gave as good results as when 5 million units were given in the same period.

2. When eight daily injections of 0.04 Gm. arsenoxide were combined with 1.2 to 2.4 million units of penicillin, the results were not significantly better than when 2.4 million units of penicillin were given alone in seven and one-half days.

3. The addition of bismuth to penicillin therapy has not significantly affected the results, provided at least 2.4 million units of penicillin were given in seven and one-half days with individual injections every two to four hours.

4. Induced fever in addition to penicillin has not significantly improved the cumulative "failure" rates when at least 2.4 million units of penicillin were given over a period of seven and one-half days.

5. When at least 2.4 million units of penicillin in aqueous solution were given in seven and one-half days with individual injections every two to four hours, the cumulative "failure" rate of patients treated for early syphilis and followed up for more than one year has been about 20 per cent.

6. Data regarding therapy given over a period of only four days are less adequate than those on the results of seven and one-half days of treatment, but such statistics as are available suggest that the cumulative "failure" rates for 2.4 million units of aqueous solutions of penicillin given in four and seven and one-half days, respectively, are not significantly different.

From the foregoing summary it is evident that the optimum total dosage of penicillin in aqueous solution in doses up to 5 million units, with individual injections every two to four hours for four to seven and one-half days, is 2.4 million units. A "failure" rate of 20 per cent is far from satisfactory but, as will be shown later, the results of this treatment were probably more satisfactory than the statistics indicate. The most satisfactory results with the use of aqueous solutions of penicillin for the treatment of early syphilis have been reported by Arnold, Mahoney, Cutler and Levitan³ who treated 728 patients with early syphilis with 40,000 units of penicillin every two hours for eighty-five injections. They reported a cumulative failure rate of only 6.65 per cent. The majority of their patients were white males who had primary syphilis. The marked discrepancy between their results and those of other clinics may well be due in part to a lower incidence of reinfections among their patients. The problem of differentiating between reinfections and relapses will be discussed later in this article.

TREATMENT OF EARLY SYPHILIS WITH POB

The use of POB in the treatment of syphilis does not require the hospitalization of patients; injections of POB need not be given oftener than once a day. Nevertheless most of the data now available on the treatment of early syphilis with POB are on patients treated for eight days while in the hospital. The cumulative "failure" rate for treatment of early syphilis with 600,000 units of POB daily for eight days has been much the same as that for 2.4 million units of penicillin in aqueous solution for seven and one-half days, viz., 20 per cent. At Bellevue Hospital the results of therapy were the same whether injections of 300,000 units were given twice a day for eight days or 600,000 units were given daily for eight days. Heller and co-authors⁴ in their most recent progress report of the treatment of early syphilis in Rapid Treatment Centers stated that the best results were obtained with two daily injections of 300,000 units of

POB for eight days, and with arsenoxide given in conjunction with aqueous solutions of penicillin; but they do not claim that the results of treatment with these schedules are significantly different from those obtained with 2.4 million units of penicillin in aqueous solutions in seven and one-half days or with single injections of 600,000 units of POB daily for eight days.

At Bellevue Hospital in October, 1947, we began to treat early syphilis with 600,000 units of POB daily for fifteen days. Of 132 patients followed up for four to nine months, only two have had to be retreated and both were probably reinfections. Although the period of follow-up is too short for evaluating this treatment, the results obtained so far are the best we have had with any schedule of rapid treatment for early syphilis for a similar period of follow-up. Chargin, Sobel, Rein and Rosenthal,⁶ of the New York City Department of Health, have recently reported on the treatment of 153 cases of early syphilis treated with 300,000 units of POB daily for sixteen days. Relapses or reinfections were noted in only about 5 per cent of the patients followed up for a period of six to ten months. Such results are superior to those obtained with eight-day schedules of treatment but it must be recognized that the data on fifteen- or sixteen-day schedules of therapy are much less complete than those on shorter periods of treatment and the two periods of treatment cannot yet be compared satisfactorily. Also, the fact that the incidence of early syphilis has steadily decreased in the past year makes comparisons of more recent schedules of treatment with those of former years difficult because the chance of reinfection is lowered by the decrease in the reservoir of infectious syphilis.

THE PROBLEM OF RELAPSE VERSUS REINFECTION

The evaluation of rapid treatment of early syphilis would be much more exact if it were possible to differentiate between relapses and reinfections in all cases. The

only convincing evidence of reinfection following rapid treatment of early syphilis is the development of a new chancre at a different site from the original one. Unfortunately, however, reinfections can undoubtedly occur without the development of a chancre. Less than 50 per cent of women who acquire a first syphilitic infection have chancres which are observed by them or the examining physician. Furthermore, a certain degree of "immunity" to the formation of a chancre is probably acquired by patients who were far advanced in the secondary stage of the disease when treatment was started. Consequently, many males as well as females may be reinfected following rapid treatment of secondary syphilis without developing a chancre but with the appearance of secondary lesions. It is even probable that some cases of serologic relapse, with no observed lesions, are actually reinfections. The histories of exposure to known cases of infectious syphilis suggest that serologic relapse may be due to reinfection in the case of some patients observed at Bellevue Hospital.

A review of all of the relapses or reinfections that have occurred among the patients originally treated with from 2.4 to 4.8 million units of penicillin in eight days at Bellevue Hospital convinces me that 40 per cent and possibly over 50 per cent were reinfections. Therefore, in my opinion, the results of eight-day schedules of therapy for both primary and secondary syphilis were actually better than the statistics indicate.

ADVANTAGES OF SHORT PERIODS OF THERAPY

Experience has proved that it is impossible to treat large numbers of clinic patients for early syphilis on an ambulatory basis when the patients have to report for daily injections for more than one week. Unless evening clinics are available, reporting for treatment means the loss of at least several hours of work. This fact together with the unreliability of many patients make ambulatory treatment with daily injections for

two weeks impractical as a clinic procedure. If we still had to rely on POB, seven or eight days of treatment would be preferable to fifteen days in most clinics.

Now that procaine penicillin G in oil and 2 per cent aluminum monostearate is available, more prolonged schedules of therapy are possible for all clinics as well as for private patients. As previously noted, two injections of 1.2 million units of this preparation, with each injection a week apart, should give much the same results as daily injections of 300,000 units of POB for fifteen days. Other possible schedules of therapy would be 600,000 units of procaine penicillin G in oil and aluminum monostearate twice a week for two or three weeks. The advantages of such therapy are obvious and the availability of slowly absorbed penicillin should prove a tremendous saving of time and money in the treatment of syphilis. If it should be found that a single treatment with 2.4 to 3 million units of procaine penicillin in oil and aluminum monostearate gave satisfactory results in 85 to 90 per cent of cases, the public health problem of treating early syphilis would be enormously aided. Treatment trucks could be sent into areas where syphilis is prevalent and patients who would not or could not report to clinics could be treated with relative ease. At present, however, the available data favor a period of treatment prolonged for at least fifteen days which would require injections of 1.2 to 2 million units of procaine penicillin G in oil and aluminum monostearate once a week for two injections. If the new preparations of penicillin in oil and aluminum monostearate are not used, the treatment of choice for early syphilis now seems to be fifteen daily injections of at least 300,000 units of POB or procaine penicillin in oil without aluminum monostearate.

TREATMENT OF RELAPSING EARLY SYPHILIS

At Bellevue Hospital the cumulative "failure" rates of patients treated with at least 2.4 million units of penicillin in eight days because of relapse or reinfection have

been similar to those of patients treated with the same amount of penicillin for original infections. It is true, however, that some patients fall into the category described by Stokes as "chronic relapsers" and they require more prolonged therapy than others. Unfortunately, it is impossible to determine in advance which patients are most likely to relapse. We have re-treated a number of patients at Bellevue Hospital two or three times for repeated relapses. In no case, however, did we find such patients resistant to penicillin. Satisfactory results were finally obtained in all of the patients who remained under observation by re-treating them with penicillin alone. Those who relapsed a second time were usually re-treated with 9 million units of penicillin in fifteen days. The safest rule to follow is to re-treat all relapses in not less than fifteen days with no less than a total dose of 6 million units of penicillin. I see no advantage in combining penicillin therapy with arsenicals or bismuth except in exceptional cases that may prove to be resistant to penicillin. We have no evidence from our data at Bellevue Hospital that the addition of eight daily injections of 0.04 Gm. arsenoxide appreciably enhanced treatment with penicillin alone.

FOLLOW-UP OF PATIENTS TREATED FOR EARLY SYPHILIS

Patients should be observed at no less than monthly intervals for one year following rapid treatment of early syphilis and at least every second month during the second year after treatment. Of the probable relapses observed at Bellevue Hospital, over 80 per cent occurred between the third and twelfth months after treatment. Quantitative serologic tests for syphilis are essential in the follow-up of patients. Serologic relapses can occur before or after the tests have become negative. Of successfully treated patients about 75 per cent became seronegative within six months after treatment. The additional 25 per cent had low quantitative tests (less than 16 Kahn units) for varying periods beyond

six months after treatment. In some cases very low titers were found for two years or more after therapy. Provided the titers remained low, retreatment of such patients did not hasten the rate at which the tests became negative. Consequently, retreatment of patients with low reagin titers six or more months after rapid treatment for early syphilis is not advised.

SUMMARY

1. In an eight-day period of therapy for early syphilis a total dose of 2.4 million units has given as good results as 5 million units.

2. When aqueous solutions of penicillin are used, individual injections should be given every two to four hours.

3. When POB is used, daily injections of 300,000 to 600,000 units are advised for fifteen days although an occasional day can be skipped and the period of treatment prolonged accordingly.

4. The cumulative "failure" rates for eight-day schedules of therapy with at least 2.4 million units of penicillin have been about 20 per cent. Many of the so-called failures were probably due to reinfections.

5. Data on fifteen-day schedules of therapy are less adequate than on eight-day schedules but the former period of treatment seems to have given better results than the latter.

6. A new slowly absorbed preparation of penicillin (procaine penicillin G in oil gelled with 2 per cent aluminum mono-

stearate) promises to simplify the treatment of early syphilis. It now seems probable that an injection of 1.2 million units of this preparation once a week for two weeks, or better, two injections of 600,000 units twice a week for three weeks will give the same penicillin action as daily injections of 300,000 units of POB for fifteen days.

7. Patients given rapid treatment of early syphilis must be observed at frequent intervals for at least two years with quantitative serologic tests for syphilis. About 75 per cent of successfully treated patients become seronegative within six months after treatment. The other 25 per cent may have low reagin titers for varying periods after six months but they do not require retreatment unless the titers show evidence of relapse or reinfection.

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Prevention and Treatment of Prenatal Syphilis*

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AN appraisal of the value of penicillin in syphilis and pregnancy is of especial interest because in this situation definitive results can be obtained in a relatively short period of observation, whereas the proper evaluation of the effectiveness of this antibiotic in other aspects of the disease may require a number of years.

SYPHILIS AND PREGNANCY

The studies to date show as conclusively as limited numbers of observed patients can show that the antepartum treatment of the woman with symptomatic early syphilis is almost 100 per cent effective in the prevention of congenital syphilis.¹⁻³ The syphilitic pregnancies in the combined reports of Goodwin and Moore,⁶ Cole et al.,⁷ Frazier,⁸ Olansky and Beck,⁹ Yampolsky,¹⁰ Ingraham et al.,¹¹ Aron et al.¹² and Thomas¹³ aggregating 609, treated with various types of penicillin and several different dosage schedules, resulted in twelve living syphilitic infants or 2 per cent failure. Some of the late miscarriages and neonatal deaths which occurred in these series were also undoubtedly due to syphilis but this is harder to evaluate. In groups in which this type of failure was studied the occurrence of late miscarriage or neonatal death among the syphilitic was found to be less than the expectancy for the non-syphilitic pregnant woman.⁶ Treatment failures have for the most part been one of two types: (1) the fetus was so grossly diseased at the begin-

ning of treatment that miscarriage resulted during or shortly after therapy and (2) the mother failed to respond to penicillin treatment for her syphilis and at times exhibited infectious relapse at or near term. The first type of failure must usually be attributed to faulty antepartum care rather than to ineffectiveness of specific treatment. The second type of failure can usually be anticipated by adequate prenatal observation of the mother and by retreatment when the recurrence occurs or in the eighth month of the pregnancy.

It has been a matter for some comment^{5,7} that small amounts of the antibiotic, grossly insufficient to cure the maternal syphilis have nonetheless resulted in the birth of a normal infant. It may be that this is merely another indication that syphilis in the incubation period is more amenable to treatment than after it becomes more firmly established. One of the great advantages of penicillin is its ability to permeate the placenta readily from the maternal to the fetal circulation in what are apparently therapeutically effective amounts in the latter months of pregnancy.¹⁴ The fetus may be treated and in some instances cured *in utero*.

When aqueous penicillin is used, there is general agreement that the maximum therapeutic effectiveness in preventing congenital syphilis is reached by total dosage of about 2.4 million units.^{2,3,6,8,10,15,16} This dosage given in amounts of 40,000 units every three hours for a total of sixty intra-

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muscular injections in eight days has given a failure rate for the infant of considerably less than 1 per cent. There is some question, on the other hand, that 2.4 million units of penicillin is the optimal dosage for best results in early syphilis in the adult. For this reason and since the cure rate in the pregnant woman is not appreciably better than in the non-pregnant woman or for men, the standard penicillin course used for early syphilis in the adult should be employed. Thomas^{3,13} recommends a total dosage of 4.0 million units for the pregnant woman with syphilis given in amounts of 40,000 units every three hours for one hundred injections. There is general agreement that arsenic and bismuth add nothing to penicillin therapy during the pregnancy and that they should not be used. Scolten¹⁷ has brought this out in an interesting manner by publishing the independent opinions from three national authorities on the best treatment for early syphilis in the eighth month of pregnancy. Although there are minor differences in detail of treatment or in the amount of penicillin to be used, none of these authorities advocates the use of arsenic or bismuth.

Some discussion has centered about the abortifacient effect of penicillin and the possibility of placental shock. Early papers¹ recommended reduction of initial penicillin dosage for the pregnant woman to avoid the possibility of miscarriage or premature labor. There was also some evidence brought forward to suggest that impurities in the original penicillin mixtures may have had some effect on the menstrual and other sex cycle functions.¹⁸ More recent experience with purer grades of penicillin have indicated that these fears are needless and that penicillin may be given to the syphilitic pregnant woman in full dosage from the start.^{6,18,19} Miscarriages or stillbirths which occur when such a course is pursued usually result from disease of the placenta or fetus so advanced to start with that there can be no hope of treatment correcting the situation.

There are several unanswered or only

partially answered problems in the penicillin therapy of the syphilitic pregnant woman. Among these are:

Ambulatory Treatment of the Pregnant Woman with Syphilis. With the exception of one study¹¹ all published reports in this field deal with the use of aqueous penicillin in symptomatic early syphilis. These procedures require such close supervision that hospitalization becomes a necessity. The initial report by Ingraham and the University of Pennsylvania group, moreover, suggested that twenty-four hour blood and tissue levels of penicillin when the oil beeswax preparations were used were too erratic to insure treatment *in utero* of the already infected fetus. They recommended that penicillin in oil wax not be used in the latter months of the syphilitic pregnancy when danger of infection of the fetus is greatest. At the time these initial studies were done there was no control of particle size of the penicillin salt and most of the methods of improving and standardizing the mixtures of the delayed action penicillins were in the experimental stage. As this study has progressed better delayed absorption penicillin preparations have become available and have been used. As a result, among the adequately followed fifty-seven syphilitic pregnancies treated with delayed absorption penicillin preparations since the above report was made not a single syphilitic infant has resulted. The failure rate in terms of living syphilitic infants accordingly stands at 1 per cent and is as good as with other forms of penicillin therapy. The usual dosage employed has been 600,000 units of penicillin intramuscularly daily for eight days or a total of 4.8 million units. Ambulatory treatment of the pregnant syphilitic woman apparently is in sight with the development of satisfactory preparations which may be given once daily or even less frequently.

When to Treat or Re-treat the Seropositive Woman with Latent or Late Syphilis. Almost all of the studies of penicillin action to date have dealt with pregnant women with recently acquired syphilis usually in the

symptomatic early stage. With these, the indications for treatment and for retreatment have been more or less clear cut and have been worked out reasonably well. Treatment is given as soon as the diagnosis is established. A single course of penicillin alone is usually effective at any time in the pregnancy. The woman is followed monthly by physical inspection for relapsing lesions and by quantitative titrated blood serologic tests for syphilis to be certain that the response is normal. The woman is retreated if infectious lesions redevelop and if the blood serologic test after an initial decrease in titer commences again to increase. It is also considered advisable to retreat in the eighth month of the pregnancy if a high sustained titer is maintained, but if the titer is falling this is unnecessary. Since the period of observation during pregnancy is short, from two-thirds to three-fourths of women who are responding normally will not have become seronegative by the time of delivery. Almost one-half of the normal (non-syphilitic) infants will consequently likewise be seropositive at birth.

With latent or late syphilis the criteria used for early syphilis in pregnancy are not applicable. Yet, upward of 80 per cent of the pregnant syphilitic women applying for medical care fall in this category. Since no open sores are present the healing of the eruption or the recurrence of lesions cannot be taken as criteria for retreatment. It is likewise customary in latent and late syphilis for the serologic response, if it occurs at all, to be slow and incomplete. If we retreated the pregnant woman with latent syphilis because of failure of serologic response we would retreat the majority of cases.

In actuality the answer to this question is not as yet available in medical literature except by inference. For the last three years at the Philadelphia General Hospital we have met this problem by giving the pregnant woman with latent or late syphilis a standard amount of treatment as for early infectious syphilis, regardless of the month of pregnancy and have not retreated them

for failure of serologic response before term, which is the usual circumstance. The treatment has consisted in 40,000 units of aqueous sodium penicillin every three hours for sixty injections for a total of 2.4 million units. Thus far 217 such women have come to term and the infants have been followed for at least six months. Two living syphilitic infants have resulted and one macerated stillborn fetus which was probably syphilitic. There were nine additional late miscarriages or neonatal deaths which could not be attributed to syphilis, not an abnormally high occurrence for the group concerned. Penicillin therapy of this group of women with latent or late syphilis has given results equal to the best that has been obtained with comparable material with symptomatic early syphilis. It seems safe to assume that empirically administered penicillin therapy as for early syphilis is also effective in latent and late syphilis complicated by pregnancy.

Retreatment of the Syphilitic Pregnant Woman in Subsequent Pregnancies Following Penicillin Therapy. The question again of retreating the pregnant woman for syphilis following penicillin is perhaps easier to answer for the expectant mother who was treated for a recently acquired infection than for the woman who has been treated prior to her pregnancy for a disease of long-standing. This is also a crucial problem in the overall picture of penicillin therapy of syphilis because pregnancy is a test of cure *par excellence* for the syphilitic woman. Since the report by Beerman and Ingraham in 1945²⁰ of the birth of a normal infant without retreatment during pregnancy in a woman who had received penicillin for secondary syphilis in December, 1943, the only statistical compilation in the literature is from the Bellevue Hospital Group in New York City. In the 1947 report of Speiser et al.³ there was one infant with congenital syphilis among eighty-six pregnancies in women treated for syphilis with penicillin prior to pregnancy but not during pregnancy. Thomas's 1948 report¹³ brings this series to 191 women with two syphilitic infants. The University of Pennsylvania

group have in process of publication a paper²¹ on this subject in which fifty-two women so handled gave birth to no syphilitic infants. This series has now been increased to eighty-eight still with no syphilitic infants appearing. Among the published cases and those known to the author there accordingly have been only two failures among 279 women in whom retreatment has been withheld.

For early syphilis the criteria for withholding treatment in subsequent pregnancies following penicillin therapy have been pretty well defined and are more or less clear cut. If the woman is seronegative or is responding normally as a result of her previous therapy, treatment is withheld. If she has relapsed clinically or serologically or if the blood serologic reagin titer for syphilis remains high, she is a candidate for retreatment. This does not answer the major problem, however, which is what to do about retreatment when the woman has been treated prior to her pregnancy for latent or late syphilis and has failed to respond serologically. In an effort to throw some light on this question we have recently withheld treatment at the Philadelphia General Hospital in all pregnant women who received what was considered to be an adequate standard course of penicillin (total dose of 2.4 million units or more) for latent or late syphilis prior to conception. Thus far forty-one of these women have come to term, 48 per cent seropositive at the time of delivery and no syphilitic infant has resulted.

It is too soon to advise withholding treatment during subsequent pregnancies in the woman who has had syphilis. If there is any reasonable doubt that the expectant mother's infection may be active, it is still better to play safe and treat. Penicillin therapy of the pregnant woman offers great hope for the infant with almost no risk for either mother or child. Yet, evidence is rapidly accumulating that the cure of the syphilitic woman with penicillin may be so complete that treatment in subsequent pregnancies will be unnecessary. There

remains the task of establishing safe criteria for withholding treatment using analyses of large series of women who have been adequately studied.

INFANTILE CONGENITAL SYPHILIS

The time to treat congenital syphilis is prenatally. The previous section has indicated that this may be accomplished almost to perfection either by preventing infection of the fetus or by treating the already diseased fetus *in utero*. With penicillin therapy as at present available only an occasional case of syphilis in an infant should occur as, when through some chance the disease is not diagnosed or adequately treated in the mother or in the rare case in which antepartum therapy fails to control the maternal spirochetemia. A few cases of infantile syphilis will still be in need of detection and treatment.

The offspring of syphilitic parents should be followed for about six months to rule out satisfactorily the possibility of congenital infection. The follow-up should consist of a blood serologic test and physical examination once monthly. A roentgenogram at four to six weeks is also of value. If the blood serologic test is positive and the circumstances of the case make infection probable, more frequent examination is desirable. In actual practice we have not found syphilitic infants in whom the diagnosis could not be established by the age of three to four months and it is usually possible much earlier even in the nursery. A normal appearing seronegative infant at six months accordingly may be considered to have escaped infection.

It has been difficult on a national basis to collect a sufficiently large number of infants with congenital syphilis to evaluate therapy adequately with penicillin. Most reports are of single cases or a few cases and will not lend themselves to detailed statistical analysis. All workers who have used penicillin either alone or in combination with other drugs in infantile syphilis are in accord that it is effective in controlling the disease, and those who have had the greatest

experience believe that penicillin alone is more valuable than previously employed remedies. The first reported cases of infantile congenital syphilis treated with penicillin are those of Moore et al.²² reporting for the National Research Council Subcommittee on Venereal Disease. This was followed by a number of reports from individuals or groups.^{1, 15, 23-34} The cases of some of these groups^{1, 15, 22, 25, 26, 27, 29, 30} were subsequently collected in the reports of Platou et al.^{3, 36, 37} so that the number of evaluated cases of penicillin-treated infantile congenital syphilis in the literature appears larger than it actually is. When these duplications are set aside, there are in the last analysis approximately 350 reported cases from which the following conclusions may be drawn as to the value of penicillin therapy in syphilitic infants. Two hundred fifty-two of these cases are those reported by Platou and his collaborators.

Within certain limitations the outcome of penicillin therapy in the infant depends more upon age and physical status at the commencement of therapy than it does upon dosage. Infants with congenital syphilis may be born prematurely, may be markedly debilitated and are easily susceptible to intercurrent infection. Such infants require hospitalization and expert supportive pediatric care in addition to penicillin. Even then, the mortality rate in the first three or four months of life is of the order of 10 to 12 per cent.^{5, 25, 36} It was at first thought¹ that the high infantile mortality rate might result from therapeutic shock incident upon the institution of penicillin therapy. Subsequent observation seems to indicate, however, that reduction in initial penicillin dosage is unnecessary and when intercurrent infection is present may actually be unwise.^{27, 30, 36} Severe febrile Herxheimer reactions do occur nonetheless in as high as from 30 to 40 per cent of the infants with active syphilis.

Our own experience has indicated that two to three years post-treatment observation is necessary to obtain the ultimate results of treatment. For this reason most

of the published reports in all of which the medical follow-up is for considerably shorter periods tend to be inconclusive and have to bridge this deficiency by such statements as "as time passes, the number of cases with unsatisfactory or uncertain results diminishes, while there is a proportionate increase in that of symptomatic and serologic cures. Changes to seronegativity are not unusual a year or more after the completion of treatment, though most babies become seronegative between four and twelve months following therapy."³⁷ In the University of Pennsylvania series of fifty surviving infants followed for an average of two years after completion of penicillin therapy given before the age of four months 100 per cent are clinically and serologically normal. Only 29 per cent were seronegative in the same period when treatment was delayed until from six months to two years. Most other workers^{10, 31, 33} have remarked upon the ready response of the young infant to treatment. Neilson and Hanchett in a recent report of the St. Louis experience³⁸ found that 100 per cent of their surviving infants treated before the age of six months were cured; 54 per cent of treatment is given between six months and one year, 26 per cent of treatment is delayed to the second year and 17 per cent in older children. Barker³⁴ quotes Moon-Adam's experience as indicating 97 per cent cures in surviving infants treated before the age of three months and about 50 per cent in infants treated from six months to two years.

Dosage generally used in the treatment of reported cases of infantile congenital syphilis has varied from 18,000 units to 98,000 units per pound of body weight. This is usually given intramuscularly in aqueous solution over a period of fifteen days in 120 injections three hours apart. As a few failures have resulted with smaller doses of the antibiotic there has been a natural tendency to increase the size of the individual dose of the total dose and of the duration of treatment. At least one authority recommends total dosage as high as 400,000

units per Kg.³⁹ While no conceivable harm can come from such a schedule, there is no indication that anything additional is to be obtained in the average infant once a dosage of 100,000 units per Kg. has been reached.

Once treatment is completed periodic observation of the infant on a one-month to three-month basis is indicated. Clinical relapse is very uncommon with infantile congenital syphilis, certainly less than 5 per cent, the reason for which has given rise to some speculation when compared with adult syphilis.⁵ Serologic relapse likewise occurs infrequently. Several reports have remarked upon the healing of the osseous lesions of infantile congenital following penicillin therapy.^{1,23,40} Rose et al.³⁰ have emphasized the increased calcification in the roentgenogram in some cases following penicillin therapy; and Hill et al.⁴¹ in one of the best papers on congenital osseous syphilis to appear in some time, have shown that the healing of infantile bone syphilis is largely accelerated by penicillin in infants under three months of age. In older infants in whom healing is a natural evolution of the disease the improvement is not demonstrably affected by penicillin therapy.

It is obvious that so short a period of observation on such a small group of infants thus far contained collectively in the literature leaves many problems of therapy still unsolved. It has not been possible to try a variety of dosage schedules. Ambulatory therapy although attempted has not been satisfactorily worked out for any considerable number of cases. Even the cure rate is only roughly estimated at approximately 73 per cent because of the paucity of reports with more than one year post-treatment follow-up. Penicillin is, nonetheless, an effective remedy and even with what we do know should replace other types of treatment for infantile congenital syphilis.

LATE CONGENITAL SYPHILIS

If the volume of cases is unsatisfactory for analysis in early congenital syphilis, this

problem is even greater for late congenital syphilis. It is to be hoped, nonetheless, that the preventative treatment of the syphilitic pregnant woman and the relative excellence of the therapy of infantile congenital syphilis will make the accumulation of examples of late congenital infection increasingly difficult. Only a few papers of importance have appeared in this field. They are the works of Yampolsky¹⁰ and Heyman,²⁹ the more recent publication of Platou and Kometani⁴² on the general subject of penicillin therapy of late congenital syphilis and Klauder's⁴³ detailed study of penicillin therapy of interstitial keratitis. The rest of the available information is fragmentary and from patients observed for too short periods to be of value in drawing conclusions.

The first reported cases of late congenital syphilis treated with penicillin are contained in the cooperative studies of the Subcommittee on Venereal Disease of the National Research Council with Stokes as spokesman.⁴⁴ Our own experience with adequately observed cases of late congenital syphilis to date comprises fifty-nine cases, six of which were latent (stigmas only), one was osseous, fifteen were interstitial keratitis and thirty-seven were neurosyphilis. The total dosage of penicillin given generally to these patients has been high, seldom less than four and usually nearer to ten million units. Our general impression has been that penicillin has been at least as good as other previously employed types of treatment. In children over six years of age the tendency is to use adult dosage schedules; in younger infants the more or less standard total dose of 100,000 units penicillin per Kg. body weight may be employed.

The serologic response generally speaking has been slow and very few patients have become seronegative as a result of treatment in the period observed. Two (33 per cent) of our six latent cases became seronegative. Twenty-five per cent of Platou's⁴² twenty-eight latent cases became seronegative. Two of our fifteen cases of interstitial keratitis

have become seronegative as compared to four among thirty-nine of Klauder's⁴³ series. In only one of our thirty-seven cases of congenital neurosyphilis did the blood serologic test become negative. A rapid serologic response to negativity is not to be expected in late congenital syphilis and perhaps is not a necessary accompaniment of such therapy.

The reported cases of congenital neurosyphilis when added to our own total eighty-five. These cases occur so infrequently in comparison with acquired neurosyphilis in the adult that there has been a tendency on the part of some workers to pool the occasional case of late congenital neurosyphilis for statistical purposes with their acquired cases. Since response of neurosyphilis to penicillin depends more upon the degree of involvement and the extent of the damage prior to therapy than it does upon the type of infection encountered, it may to some extent be artificial to consider late congenital neurosyphilis in a separate category. Nonetheless, an analysis of existing information is made for what it is worth.

There is general agreement that, as with acquired adult neurosyphilis, there is a rapid spinal fluid response particularly in the asymptomatic cases. In seventeen of our group of twenty-seven followed for periods varying from six months to four years after therapy the spinal fluid became negative. In Platou's group, apparently largely asymptomatic, followed for more than twenty-four months, four of thirty-four originally positive spinal fluids remained abnormal. In active juvenile paresis,³¹ optic atrophy and eighth nerve deafness^{29,44} progression commonly occurs after the institution of penicillin therapy. This again may not be an indication of the ineffectiveness of the treatment since it occurs after other modes of therapy including fever, but may be a natural evolution of the disease with fibrous tissue replacement of the already damaged area. Although the number of cases available for analysis is too small to make any general conclusions, maximal therapy with penicillin in the

magnitude of ten million units over a period of fifteen days with repetition if necessary should be employed in late congenital neurosyphilis, and fever therapy should be considered in addition to penicillin if initial response is not satisfactory.

The thirty-seven cases of *interstitial keratitis* from late congenital syphilis contributed by various authors, including our own fifteen patients, add very little to the detailed and well controlled report of Klauder's fifty-nine cases. Since Klauder's report represents a cooperative study to which he contributed from his own resources only forty-one patients, there may be some duplication even in the reported ninety-six cases in which penicillin was used. Penicillin does not exert an immediate favorable effect on active interstitial keratitis. Like metal chemotherapy it does not prevent an initial attack of interstitial keratitis, nor involvement of the second eye nor recurrence of the disease in the previously affected eye. Klauder believes that fever therapy is still the treatment of choice for interstitial keratitis and that, while penicillin has produced results thus far neither better nor worse than metal chemotherapy, it is probably the best adjunct treatment to be employed with fever. Total dosages employed have ranged from 2.4 to 6.0 million units. *Clutton's joints*, which frequently accompany or precede interstitial keratitis, are similarly not immediately favorably influenced by penicillin.^{29,43}

CONCLUSIONS

Penicillin has been found to be effective in the prevention and treatment of congenital syphilis and, except perhaps for interstitial keratitis, may completely replace all other forms of specific therapy. It is of greatest value in this field when given to the mother either prior to conception or in the early months of her pregnancy. It is effective in the cure of the fetus *in utero* if the disease is not too far advanced. It is very effective in curing the newborn syphilitic infant if he is not already in a

hopeless state of debilitation. It becomes decreasingly valuable in producing complete cure of congenital syphilis during late infancy and childhood but remains at least on a par with metal chemotherapy.

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Penicillin in Benign Late and Visceral Syphilis*

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FOR the purpose of this discussion, benign late syphilis may be loosely defined as allergic in type, with chronic, focal inflammatory lesions involving structures not essential to life or vision, and which develop more than two years after infection. In the great majority of patients such lesions involve the skin or mucous membranes (late nodular syphilides, cutaneous or mucosal gummas), the bones (periostitis, osteitis, osteomyelitis) or the muscles or tendons (gummas of muscles, synovitis). Infrequently, patients with the allergic tendency develop gummatous lesions in such important viscera as the liver, spleen, stomach, lungs or testes. Gummatous involvement of the cardiovascular or central nervous systems is rare; and in these situations the granulomatous process may constitute a direct and immediate threat to life. In effect this communication, therefore, resolves itself into a consideration of the effects of intramuscularly administered penicillin on the mucocutaneous, osseous and visceral manifestations of late acquired syphilis, manifestations which, however painful, disabling or disfiguring, seldom if ever kill the patient. The material to be presented represents a review of the literature together with an analysis of the records of the Syphilis Clinic, Department of Medicine, the Johns Hopkins Hospital, including data previously published.¹

The mode of action of penicillin in benign late syphilis is not entirely clear. The therapeutic activity of the antibiotic, aside from an ill-defined "general tonic effect," probably rests on its direct bactericidal (i.e.,

treponemicidal) action. The typical gummatous lesion is a chronic, focal granuloma with central caseation necrosis. Although *Treponema pallida* are seldom demonstrated in these lesions, it is believed by many that the organisms develop about a focus in an individual who has become sensitized or allergic to the parasite or to its by-products. This hypothesis would explain nicely the healing of gummas following the administration of treponemicidal drugs such as arsenic, bismuth or penicillin; it may not explain the occasional lesion which responds to one but not another type of syphilotherapy. Whatever the mode of action of penicillin, in our own experience and in the results reported in the current literature it has proved to be an effective remedy in the treatment of the vast majority of patients with clinical manifestations of benign late syphilis.

Mucocutaneous Benign Late Syphilis. In the early clinical evaluation of penicillin these manifestations of late syphilis were unique in that they could be observed or palpated directly and measured accurately, and the difference between treatment success and failure could be objectively determined. In our own study, for example, we have applied the following criteria for "complete healing": In ulcerative cutaneous gummas we required restored continuity of the skin surface by complete epithelialization and the disappearance of signs of inflammation. Nodular gummas were regarded as healed when swelling, induration and erythema had vanished, although pigmentation might persist. Per-

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forating gummas of the palate were considered healed when the integrity of the mucous membrane had been restored or the residual perforation was completely quiescent and not inflamed or indurated. The use of these or similar criteria enabled investigators to report comparable data.

The first case report² described a patient with a nodular syphilide of the nose who was treated with 320,000 units of amorphous penicillin; the lesion healed leaving only residual pigmentation. In 1944 a group of investigators³ reported on twenty-one cases of benign late syphilis of skin and bones (not separately considered). They found that the lesions healed in twelve to forty-six days under a dosage of approximately 300,000 units and concluded that results were so satisfactory that little further investigative interest or effort was required. In spite of this optimistic conclusion, there were two failures in the group studied: One was a suspected gumma of the orbit and no particulars were given concerning the other.

A year later O'Leary and Kierland,⁴ without citing details, wrote that "penicillin is by far the outstanding remedy for the treatment of late cutaneous and osseous syphilis." They recommended two courses of 2.4 million units each, given four months apart. Stokes and his co-workers⁵ stated that penicillin in low dosage (300,000 to 600,000 units) cured soft tissue gummas and simple uncomplicated bone lesions. Inadequate data were given concerning the diagnosis and treatment of patients having a satisfactory outcome but one treatment failure was reported. The patient had received arsenobismuth therapy for gummatous osteomyelitis of the sinuses and frontal bone without apparent effect; penicillin administration (2.4 million units in ten days) likewise failed to give improvement during 101 days of post-treatment observation. Hill⁶ mentioned a patient with an extensive destructive gumma involving the center of the face, including the nasal septum and hard palate, who was unimproved after 2.4 million units of penicillin.

Therapy with induced tertian malaria completely resolved the lesion. Hahn⁷ has reported in detail a patient given 4.8 million units of amorphous penicillin for a large granulomatous penile mass which failed to improve. This lesion was likewise unresponsive to therapeutic dosages of tartar emetic and sulfonamide compounds. It had clinical attributes of a gumma and microscopic examination of a specimen taken for biopsy revealed "chronic inflammatory tissue of a nonspecific nature." Ten months after penicillin administration arsenobismuth therapy was given with prompt and complete healing.

The first reported experience from this clinic¹ described results of penicillin treatment in eighteen patients with gummas of the skin and/or mucous membranes. It was found that total doses greater than 1.7 million units of amorphous penicillin gave progressive improvement in most instances. One patient given only 60,000 units during her first course of therapy developed renewed activity in the scar one year later. There were no signs of relapse when last seen 805 days after retreatment with 1.2 million units. A diabetic patient with secondarily infected gummatous leg ulcers and arteriosclerosis of the lower extremities also required retreatment. The lesions failed to heal after 1.2 million units; 106 days later he was given 2.0 million units of penicillin with complete healing within one month. He remained well for seventeen months when a recurrent nodulo-ulcerative syphilide appeared in one of the scars. The administration of 8.0 million units of penicillin G in ten days and a prolonged course of arsenobismuth therapy promoted rapid healing. The other sixteen patients originally reported have undergone no relapses during follow-up periods as long as 1,596 days (mean, 911 days) although one received an additional 10.0 million units for serorelapse; the lesions had remained healed for 541 days at the time of retreatment.

Since the original communication we have treated with penicillin alone sixteen additional patients with cutaneous and/or

mucous membrane gummas. Total dosages ranged from 0.32 to 7.0 million units; ten received crystalline penicillin G. All have been treatment successes in that our criteria of healing were satisfied. The mean period of post-treatment observation, however, has been only 364 days. In the total series of thirty-four cases the gross incidence of failure was 5.9 per cent.

One report⁸ has appeared on the treatment of a nodular late syphilide with 7.8 million units of oral penicillin administered over a ten-day period with a satisfactory outcome.

Conclusions. According to Moore⁹ there appears to be general agreement that the older methods of syphilotherapy were usually successful in producing rapid healing of skin and mucous membrane lesions, even the largest cicatrizing within forty-two to fifty-six days. As nearly as can be estimated from available data, penicillin, if it is to be effective at all, will likewise promote at least temporary healing in less than two months. There is no good evidence that the rate of healing is more or less rapid following penicillin; nor is there available sufficient material to justify opinion as to the comparative effects of amorphous penicillin and crystalline penicillin G.

Sufficient evidence is at hand to show that a single course of penicillin therapy will not induce prompt healing or prevent gummatous recurrence in all patients with cutaneous and/or mucous membrane gummas. Although there is unquestionably a tendency to report promptly penicillin failures rather than successful results, it would seem from these data that in 5 to 10 per cent of these patients retreatment with penicillin or institution of arsenobismuth therapy would be indicated. As a corollary, too much reliance should not be placed on a single course of penicillin administration as a therapeutic test in benign late mucocutaneous syphilis.

Benign Late Osseous Syphilis. The early reports already cited³⁻⁵ have to a great extent classified benign late syphilis of skin and mucous membranes and of bone

together because they are frequently co-existent (e.g., gumma of skin with underlying periostitis of tibia). The criteria for successful treatment differ markedly between the two groups. Whereas the former heal *actively*, a treatment success in late syphilis of bone is usually characterized by arrest or lack of further activity. Serial roentgenograms show that proliferative or destructive activity has ceased; occasionally areas of osseous destruction are repaired completely. Where bone surfaces are near the skin (e.g., tibia, skull) and the overlying soft tissues are involved in a gummatous process with or without secondary infection, it may be impossible to tell what degree of osseous involvement is due to syphilis of soft tissues and how much to the process in the subjacent bone. In short, the division between success and failure of treatment is less sharply delineated, and serial observations over a prolonged period of time must be made before conclusions are justified.

In addition to the five patients with osteitis, osteomyelitis and/or periostitis described in our first report¹ we have since treated eleven more. Dosages of penicillin from 0.6 to 7.0 million units were given; five patients received penicillin G. Post-treatment observation periods ranged from 135 to 1,449 days (mean, 706 days). In only five of the sixteen patients studied were bone lesions unaccompanied by gummatous involvement of the overlying soft tissues. In most cases initiation of penicillin treatment caused a dramatic cessation of local deep bone pain in osseous syphilis. (This was also true following arsenic, bismuth and, occasionally, iodides.) One exception was noted in our series. A twenty year old negress with periostitis of the tibiae and fibulae gave a history of severe osteocopic pain of five months' duration. The deep pain in the legs was essentially unchanged following 0.6 million units of penicillin and two months later similar pain began in the right arm. Roentgenograms showed thickened cortex and irregular contour of the right ulna. Without additional antisiphilitic treatment the attacks of ostealgia in all sites

gradually became less severe and troublesome, disappearing entirely during the seventh post-treatment month. These pains have not recurred and roentgenograms taken at 1,109 days showed a static process in the involved bones.

The end results in these sixteen patients, in terms of disappearance of symptoms referable to the skeletal system and roentgenographic evidence of osseous arrest or repair, were all adjudged to be satisfactory. One unusual treatment failure, however, deserves special mention. A nineteen year old negress with syphilitic osteomyelitis and periostitis of one radius was treated with 1.62 million units of amorphous penicillin. Although this lesion responded nicely, eight months later a typical nodular serpiginous syphilide of the forearms and hand appeared. A specimen for biopsy was described (Dr. L. W. Ketron) as characteristic of tertiary syphilis and arsenobismuth therapy was instituted.

We have treated two patients with uncomplicated syphilitic osteomyelitis with a satisfactory outcome in each following 1.0 and 1.62 million units of amorphous penicillin, respectively. Miller¹⁰ has reported a case similar to ours in which clinical, pathologic and roentgenographic evidence was presented. Following 2.4 million units of penicillin the pain subsided, the patient gained weight and roentgenograms showed improvement; sequestrum formation was not present. The case of Stokes⁵ responded neither to arsenobismuth treatment nor to penicillin; presumably sequestra were present.

Whether or not results of penicillin administration in patients with Charcot joints properly belong in this discussion, it may be briefly said that penicillin exerts no appreciable beneficial effect.^{5,11}

Conclusions. Although the cases thus far reported concerning penicillin in benign late osseous syphilis are relatively few in number, results appear to be satisfactory in the patients with uncomplicated periostitis, osteitis or osteomyelitis. Syphilitic osteomyelitis with sequestrum formation appears

to respond poorly to treatment and probably requires a combined attack by the surgeon and syphilologist for best results. When there is extensive gummatous involvement of adjacent skin or mucous membrane,^{5,6} results of treatment with penicillin alone may be disappointing. The clinician faced with the patient with extensive gummatous involvement of the nasopharynx and paranasal sinuses may be wise in prescribing penicillin plus metal chemotherapy and/or fever.

Gummatous Visceral Syphilis (Excluding Cardiovascular and Neurosyphilis). Active late syphilis of the liver is a condition rarely demonstrated clinically. The initial and essential lesion is the gumma which arises in a highly localized or focal manner and on healing leaves a stellate scar. Because of the great functional reserve and capacity for regeneration of this organ, symptoms or signs of hepatic insufficiency are rare. Clinical observations, laboratory and roentgenographic studies do not permit more than a presumptive diagnosis. To prove the presence of active hepatic gummas two procedures are available. The more reliable (but somewhat dangerous) method is to take a specimen for biopsy. The second is the therapeutic test which requires a post-treatment observation period of months or years.

The only report¹² dealing with this type of benign late syphilis described a satisfactory result in each of two patients (one with late congenital syphilis) with gummatous hepatic syphilis treated with 3,200,000 and 920,000 units of amorphous penicillin. These patients have remained well over observation periods of 487 and 1,449 days, respectively.

We have not treated a patient with late gastric syphilis with penicillin in this clinic. Knight and Falk,¹³ however, report clinical, gastroscopic and pathologic data on a fifty-four year old white male who was given "intensive antisiphilitic therapy" (dosage not specified). Although clinical, roentgenographic and gastroscopic studies all showed definite improvement, partial gas-

trexotomy was performed. The pathologic picture was compatible with gastric syphilis. *T. pallida* organisms were not demonstrated.

Benign late pulmonary syphilis is seldom demonstrated clinically. Kulchar and Windholz¹⁴ reviewed the available literature (pointing out that *T. pallida* have been demonstrated in only two instances), and presented one patient treated with penicillin. A twenty-nine year old white male had syphilitic bone involvement in three sites, an area of increased density in the left lung field, together with a pleural exudate on that side. Following 2.5 million units of penicillin, bone pain subsided and less than one month later the exudate had disappeared and the area of density had been replaced by fibrosis and increased parenchymal markings. No pathologic evidence was presented. A more convincing case recently came to our attention. This patient had a large globular mass in the right lung which failed to respond either to penicillin or to metal chemotherapy given in another clinic; it increased in size during treatment. Pneumonectomy was done since such thorough therapy with no resulting improvement was believed by the attending physicians to be strong presumptive evidence of neoplasm. The gross specimen showed central caseation necrosis, and sections for microscopic study were examined by competent pathologists who believed that the diagnosis of gumma was the most probable one.

Conclusions. It is obvious that involvement of the viscera by a gummatous process represents a considerable, and sometimes insurmountable problem in diagnosis; it may be even more difficult to adjudge the results of a given therapeutic method. It is in this situation that the qualities of penicillin appear to recommend it particularly. In contrast to the older methods of syphilotherapy, penicillin treatment is brief and essentially free of risk. Since, as far as the therapeutic test is concerned, the treponemocidal properties of a given drug appear to be most important, penicillin probably yields a definite answer as frequently as metal chemotherapy. When roentgeno-

graphic evidence of disease is being considered (e.g., possible gumma of lung), it must be kept in mind that penicillin is bactericidal for many organisms. We have had the experience of seeing a solitary area of increased pulmonary density resolve promptly following administration of penicillin. Although the patient had gummatous lesions elsewhere, in retrospect it was impossible to rule out non-syphilitic disease, such as a patch of bronchopneumonia.

Gummatous Keratitis. The keratitis pustuliformis profunda of Fuchs is the only type of corneal syphilitic disease to show a spectacular response to older types of anti-syphilitic therapy.¹⁵ It has shown an equally satisfactory response to penicillin in the only case thus far reported.¹

COMMENTS

From the practical standpoint, benign late gummatous syphilis of skin, mucous membranes and of bone are the most important types. In this series of thirty-nine patients with one or more of these manifestations, a single course of treatment with penicillin alone yielded satisfactory results in all but three. These failures were: (1) recurrence of cutaneous gumma, (2) initial failure to heal promptly after a second course of penicillin, followed by recurrence of cutaneous gumma and (3) initial appearance of a nodular syphilitic eight months after penicillin therapy of late osseous syphilis. The only comparable series published,³ in which twenty-one patients with benign late syphilis of skin and bone were treated with penicillin alone, mentioned two treatment failures. The gross incidence of failure in the combined material was 8.3 per cent (five failures among sixty patients studied). This figure is sufficiently large to show that caution must be used in the interpretation of the therapeutic test in benign late syphilis.

Total dosages employed in our series ranged from 60,000 to 7,000,000 units. In general, the patients treated earlier received smaller dosages. No failures were encountered in the eleven patients treated with crystal-

line penicillin G. This was probably due to two factors, both associated with the recent availability of this product. First, larger total dosages were employed and, secondly, post-treatment observation periods have been shorter. There is no real evidence as yet that crystalline G is superior to amorphous penicillin in the treatment of benign late syphilis.

The majority of our patients with benign late syphilis also had recognizable syphilitic disease involving the cardiovascular or central nervous systems. Twenty-three had neurosyphilis and in one of these a saccular aortic aneurysm was also found. Eighteen had late asymptomatic neurosyphilis, three had tabes dorsalis and two had unclassified late meningovascular neurosyphilis. The two patients in the last category and one with asymptomatic neurosyphilis had "active," group III cerebrospinal fluids (Dattner-Thomas); in the remainder the cell count and protein values were within physiologic limits and the major abnormality noted was the positive Wassermann reaction with relatively large volumes of cerebrospinal fluid (0.2 to 1.0 cc.). These abnormal fluids responded to penicillin administration in the usual fashion. Elevated cell counts and protein contents rapidly fell to normal; the colloidal mastic and Wassermann tests responded more slowly. Laboratory evidence of neurosyphilis disappeared during the periods of observation in eleven of the patients with group II cerebrospinal fluids. In one patient eight positive or doubtful spinal fluid Wassermann reactions in low dilutions were reported before the first entirely normal one taken 1,385 days after penicillin therapy. None of the "inactive" fluids became worse during the period of observation. Serologic blood titers were more recalcitrant. One patient was seronegative before and after treatment. The other thirty-eight patients were seropositive at the time of the most recent observation and in eleven of these the most recent titer was higher than the pretreatment one. These data merely emphasized the fact that most patients with symptomatic late syphilis

were seroresistant and that penicillin was no more effective in reversing the serologic reaction to negative than have other types of syphilotherapy.

In our experience the febrile Jarisch-Herxheimer reaction did not seem to be associated with particular types of gummatous lesions. A rise in temperature over 100.4°F. within the first twenty-four hours after the initiation of therapy was noted in five patients; the highest fever was 103.2°F. All these patients had "inactive" cerebrospinal fluids. Fever in excess of 100°F. was noted in two of the three patients with group III, six with group II and in two patients with normal pretreatment cerebrospinal fluids. In a single instance only was significant increase in local erythema and swelling noted. One patient with a gumma of the left vocal cord (and of the hard palate and nasal septum) suffered no ill effects following initiation of therapy with the usual doses (100,000 units every three hours).

SUMMARY

The current literature dealing with the use of penicillin in benign late syphilis of skin and mucous membranes, the bones, liver, stomach, lungs and cornea is briefly reviewed. On the basis of reported data and an analysis of our own material satisfactory results may be obtained in approximately 90 per cent of such cases by the administration of a single course of penicillin alone.

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Significance of Spinal Fluid Findings in Neurosyphilis*

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THE importance of serologic tests for syphilis (STS) is recognized by everyone working in this field. In early syphilis, for instance, not only disappearance of clinical signs and symptoms but also the reversal of the positive STS to negativity is the therapeutic goal. In late syphilis, however, there is quite often considerable doubt whether positive STS indicate the continuation of the syphilitic process or whether they represent solely a harmless residual of a formerly active infection. Although the routine application of quantitatively standardized serologic tests has greatly contributed to a better understanding of the activity of the syphilitic process, it still leaves the problem of the so-called Wassermann-fast cases unexplained.

Fortunately, in neurosyphilis the evaluation of the character of the underlying process is not dependent only on the specific tests for syphilis. Additional information can be obtained by other commonly performed examinations of the spinal fluid, i.e., the cell count, total protein determination and colloidal tests. It is a clinically well established fact that most infectious processes involving the meninges give rise to a pleocytosis. Inasmuch as the meninges may be invaded by spirochetes in the early stages of syphilis, it is not surprising that pleocytosis is the first sign of syphilitic involvement of the central nervous system (Ravaut,¹ Sicard²). With arrest of the syphilitic process the abnormal cell count quickly returns to normal. It is the most labile element of the spinal fluid syndrome as observed by all investigators interested in establishing a

correlation between pathologic process and spinal fluid findings. This rapid subsidence of pleocytosis following successful treatment occurs in all forms of neurosyphilis. It was first noted after malaria therapy of general paresis in Wagner-Jauregg's clinic in Vienna and later confirmed by all authors reporting the effect of malaria treatment on the spinal fluid in neurosyphilis. If the syphilitic process has been definitely arrested, there is no recurrence of pleocytosis, as has been demonstrated by the follow-up of many patients with neurosyphilis over a period of more than fifteen years (Dattner³). Pleocytosis, therefore, constitutes the best criterion of the activity of syphilis of the central nervous system.

Next as a guide for determining the trend of the syphilitic process is the spinal fluid total protein estimation. With the new electrophotometric method of determining the turbidity of fluids, measurements of the protein content of the spinal fluid can be performed with a high degree of precision. Values so obtained can be duplicated without difficulty. It is, therefore, possible to observe changes in the pathologic process in the central nervous system by comparing total protein determinations over long periods. As with the cell count, the total protein values follow closely the intensity of the inflammatory-degenerative alterations of the nervous tissues. Effective treatment manifests itself in a gradual decrease in protein whereas patients who relapse following treatment exhibit increasing amounts of total protein on repeated tests.

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Finally, additional support in estimating the efficacy of treatment is given by the colloidal tests. They were originally designed only for the differentiation between the various globulins and albumins constituting the total proteins. As long as the colloidal solutions could not be standardized no reproducible results were obtainable and, therefore, no comparisons could be made in the follow-up of patients. Since Lange's⁴ introduction of a new technic of his colloidal gold test, however, it has become possible to obtain quantitative as well as qualitative information concerning the nature of the syphilitic process. The constant color changes of the gold sol, which are expressed in numerical values, can now be totaled and furnish a quantitative standard. Following successful treatment there is not only a change in the character of the curve but also a decline in the sum total of the color figures.

These four tests of the spinal fluid give much more accurate information about the syphilitic process than does the detection of reagin alone even when quantitative determinations are made. Each test represents a different and independent approach toward this goal and yet the end results form a syndrome which permits a reasonable interpretation. If the neurosyphilitic process is progressing, we observe pleocytosis, positive specific tests for syphilis, increased total protein and abnormal colloidal reactions. If the pathologic process is abating or comes to a standstill, we have correspondingly normal cell counts and decreasing values in the other tests until finally all of the tests become normal. In permanently arrested cases of long standing it may require five or more years for the Wassermann and sensitive colloidal gold reactions to become completely normal.

This gradual improvement of the abnormal spinal fluid syndrome following successful treatment has been reported by the author in many papers since 1928.⁵ In 1942 Dattner and Thomas⁶ generalized their observations on patients treated for neurosyphilis at Bellevue Hospital as follows:

A positive spinal fluid Wassermann reaction does not prove activity of the syphilitic process. When a positive complement fixation test of the spinal fluid is associated with pleocytosis and/or increased protein, activity must be assumed. If the spinal fluid tests show normal cell count and definite diminution in protein content six or more months after treatment has been discontinued, the activity of the syphilitic process in the central nervous system in all probability has been permanently checked although it may require years before the complement fixation and colloidal tests become completely negative.

It is regrettable that in the past the attention of many physicians was focused almost exclusively on the complement fixation tests of the spinal fluid in evaluating the effectiveness of treatment. This resulted in a misconception of the relationship between the spinal fluid findings and the syphilitic process in the central nervous system. A positive serologic test of the spinal fluid following treatment was taken as evidence of the persistence of the infection. As a result, antisyphilitic therapy was continued in many cases in the hope of reversing positive Wassermann reactions to negative. If the concept of the parallelism between the pathologic process and the spinal fluid syndrome as described above had been correctly understood, many patients would have been spared unnecessary and sometimes hazardous and expensive treatment.

SUMMARY

Activity and arrest of the neurosyphilitic process are reflected in the spinal fluid findings. This can be demonstrated by repeated examinations of the spinal fluid which should include a cell count, quantitative tests for total protein, the complement fixation reagin titer and Lange's new colloidal gold reaction.

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Current Status of Penicillin Therapy in Neurosyphilis*

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IN 1943 Mahoney, Arnold and Harris¹ reported that penicillin was an active spirocheticide and an effective agent in the treatment of early syphilis. Almost immediately penicillin was tried in the treatment of the various forms of neurosyphilis. Here again it was demonstrated to be efficacious. In most cases of asymptomatic neurosyphilis and syphilitic meningitis the drug cleared up the cerebrospinal fluid in a very short time and relieved the symptoms of meningitis. (It should be borne in mind that this type of neurosyphilis has responded well in many instances to almost all forms of arsenical treatment and very well indeed to fever.)

The problem remaining after the first survey of penicillin was that of adequate dosage. It soon became evident that an aqueous solution of amorphous penicillin, 3 million units given over a period of seven to fifteen days at six-hour intervals, was likely to give a favorable outcome in a great majority of cases. This conclusion was arrived at by trying a number of schedules differing in the amount of penicillin administered and the duration of the course and the time interval between injections. The development of new forms of penicillin, such as the slowly absorbed forms of penicillin like procaine penicillin in oil, has made it difficult to be more specific than this about dosage at the present time.

General Paresis. The problem of the best form of treatment for the more destructive forms of neurosyphilis (general paresis and tabes dorsalis) was not so readily arrived at; in fact, there is at this time a considerable

difference of opinion among various investigators. It early became evident that in general paresis penicillin was remarkably effective in improving the spinal fluid abnormalities. Three million units of the drug at six-hour intervals over a two-week course almost invariably produces in the course of three to six months a marked reduction in the spinal fluid cell count and total protein. However, with the dosage limited to 3 million units, spinal fluid relapse takes place in not a few cases, suggesting that in all probability the cerebral syphilis had not been adequately controlled. On the basis of such relapsing tendencies the dosage was increased by most investigators to 6, 9 and 12 million units. Other investigators gave repeated courses of penicillin, with an interval of one month or more between the courses.

Another question about the effectiveness of penicillin in the treatment of general paresis relates to the improvement of the psychotic state when this exists. There is a great difference of opinion about this. Reports from the Mayo Clinic,² Johns Hopkins³ and the Boston Psychopathic Hospital⁴ indicate that the psychologic response of the parietic psychosis is by no means as good when penicillin alone is relied upon as when fever treatment is given. On the other hand, investigators at the University of Pennsylvania Clinic⁵ and Bellevue Hospital⁶ are strongly of the opinion that the clinical results are equally good if not better with penicillin alone. The Michigan group⁷ first reported that the psychosis did not respond as well with

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penicillin as with fever but more recently have concluded that penicillin-treated patients respond as well as those treated with malaria. Reports from other clinics are equally divergent. This is very reminiscent of the difference of opinion which has occurred over the years as to the relative effectiveness of tryparsamide, malaria and mechanically produced fevers. After exhaustive studies over a period of more than twenty years no uniformity of opinion was reached. It therefore is not surprising that opinions should differ with regard to penicillin and it is probable that general agreement will not be attained in the course of a number of years.

At the Boston Psychopathic Hospital most of the patients with general paresis have been treated with a combination of penicillin and a short febrile course. The conclusion of the workers at this clinic is that a course of 6 to 9 million units of crystalline penicillin G, given at six-hour intervals over a period of fifteen days, and used in conjunction with approximately half of the standard febrile course, is an effective means of treating most patients with general paresis. At this clinic it is customary to induce from five to seven malarial paroxysms concurrently with the use of penicillin for those paretic patients who are in good physical condition. For other patients of this group who have systemic disease or marked debility the fever box is used concurrently with penicillin and the patient is given a total of approximately twenty hours of fever between 104° and 105°F. This relatively small degree of fever is not hard on the patient and his general condition at the end of the course of treatment is usually excellent.

The Johns Hopkins group³ are of the opinion that cases of general paresis are better treated by a full course of fever in addition to relatively large amounts of penicillin. At any rate, the combination of 6 to 9 or 12 million units of penicillin and a course of fever results almost invariably in a reduction of the spinal fluid cell count and total protein to normal within a period

of three to six months, and in most instances spinal fluid relapse does not take place. Spinal fluid serologic and colloidal tests are much slower in the return to normal and follow a time schedule that is quite similar to that observed in malarial treatment, that is, approximately 10 per cent of the cases have a normal spinal fluid at the end of a year and each succeeding year adds 10 per cent to the group with normal fluids.

However, despite the combination of penicillin and fever, there are some patients with paretic psychosis who fail to improve mentally. This is similar to the experience with other forms of treatment of this disorder. Recent studies in our clinic indicate that the clinical response is dependent in part upon the mental syndrome, that is, patients with a clinical picture of the simple dementing type, depressions or mild elations improve rather quickly, whereas patients who present symptoms similar to those seen in schizophrenia or paranoid states are likely to have a continuation of the psychosis despite satisfactory improvement of the cerebrospinal fluid and other evidence of arrest of the disease.

A point of some interest is that electric shock therapy affects the psychosis associated with general paresis in much the same fashion as in so-called functional psychoses. Very disturbed, agitated paretic patients who fall into the group that we have conveniently called "galloping paresis" may be quickly brought to a state of mental improvement by the use of electric shock therapy, and certainly in some instances life may be saved thereby.

It has been noted that paretic patients treated by a full course of malaria are more likely to develop auditory hallucinations, which may be long persistent, than patients who are not so treated. With the use of penicillin some evidence has been accumulating that there may be a greater possibility of patients developing persistent paranoid states than in patients not so treated.

All this means that treatment of the psychosis of general paresis requires not only specific treatment of the syphilitic

meningoencephalitis but also considerable attention to the total psychiatric treatment.

Tabes Dorsalis. The evaluation of treatment in cases of tabes dorsalis is a matter of great difficulty. Tabetic cases have a tendency to "burn out," that is, with the passage of time a considerable number of the patients with this disease develop normal spinal fluids indicating an arrest of the syphilitic process. On the other hand, symptoms may persist or increase in intensity despite apparent arrest of the inflammatory process. Penicillin has proved to be extremely effective in bringing the spinal fluid to normal in cases of tabetic neurosyphilis; 3 to 6 million units of crystalline penicillin G in a two-weeks' course almost invariably is sufficient to produce a normal spinal fluid. However, with this type of treatment as with the treatments in the past, symptoms may not be greatly relieved. A general working rule is that if one is dealing with relatively acute cases of tabes the symptoms may be greatly alleviated if not completely removed in about 50 per cent; whereas in the other 50 per cent the symptoms continue despite a "spinal fluid cure." The evidence at hand suggests that penicillin produces about the same symptomatic results as were obtained with fever treatment.

Syphilitic Optic Atrophy. There is not enough experience yet available to allow definite conclusions as to the effectiveness of penicillin in syphilitic optic atrophy. There is suggestive evidence, however, that penicillin does produce striking results in arresting the progress of optic atrophy in not a few cases. It is probable that the combination of malaria and penicillin is the most effective treatment now available. It will take a number of years to determine the permanency of apparent arrest and it will also be some time before enough patients are treated to allow one to make any definite statements as to the percentage of the cases that may be halted. Encouraging results have been reported on the treatment of acute syphilitic auditory nerve deafness.

Meningovascular Neurosyphilis. Meningovascular neurosyphilis responds, from the

laboratory standpoint, much as asymptomatic neurosyphilis and meningal neurosyphilis. In most instances a course of 6 to 9 million units will arrest the syphilitic disease. The clinical results, of course, depend upon the amount of brain damage that has occurred.

Various forms of spinal syphilis can be arrested by the use of penicillin and the clinical results will depend upon the amount of vital tissue damage that has taken place. Congenital neurosyphilis responds in much the same way as the similar underlying pathologic process in cases of acquired neurosyphilis.

CONCLUSIONS

Penicillin has proved effective in the treatment of all forms of neurosyphilis. Proper dosage and the place of adjuvant treatments have not been completely settled at this time, the changing forms of penicillin complicating establishment of a definite routine of treatment.

Using crystalline penicillin G as a standard for comparison with other forms of penicillin, it may be stated that with this preparation syphilitic meningitis responds well to approximately 6 million units given every six hours for ten to fourteen days. Most cases of asymptomatic, meningitic, meningovascular and tabetic forms of neurosyphilis likewise respond to this schedule of treatment, the cell count and total protein of the spinal fluid becoming normal within three months, certainly within six months. If not, further treatment should be given. The serological tests and the colloidal tests will usually be within normal limits in the course of a year. While Dattner and Thomas⁹ state that as long as the cell count and total protein remain normal the disease is in control, nonetheless if the serologic and colloidal tests do not show improvement at the end of a year after conclusion of treatment, it would appear wise to give further treatment.

Meningovascular neurosyphilis responds much the same as the other forms men-

tioned. General paresis is more resistant to penicillin treatment.

Opinion differs as to whether one should depend upon penicillin alone or add fever therapy. If penicillin alone is used, the dosage should be 9 to 12 million or more units over a period of at least two weeks and the cerebrospinal fluid should be re-examined every few months. If the cell count and total protein do not remain normal, further treatment is necessary.

In the opinion of the writer the combination of penicillin and fever is more likely to result in a permanent arrest and to give more assurance that relapse will not occur.

In some instances of paretic psychosis electric shock therapy may be indicated to control the psychosis.

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Venous Thrombosis and Pulmonary Embolism in Tuberculosis*

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THE recent wave of adverse criticism directed against the use of bed rest as a therapeutic procedure has exerted a profound effect on all phases of American medicine. The surgeon,^{1,2} cardiologist,^{3,4} psychiatrist,⁵ obstetrician⁶ and, more recently, the phthisiologist⁷ have all deprecated its widespread use. This revolt against one of the oldest and most widely accepted therapeutic measures was occasioned by the fearsome and tragic annual loss of life caused by pulmonary embolic accidents. Inasmuch as the source of embolism is almost always venous thrombosis and as the latter is often associated with enforced recumbency, the value of bed rest as a therapeutic agent is receiving renewed and justifiable attention.

There can be no argument with those surgeons^{1,8-14} who have demonstrated the effectiveness of early mobilization of the postoperative patient. In like manner, both Harrison³ and Dock⁴ have indicated the hazards of bed rest in patients with cardiovascular disease.

In 1923 Krause¹⁵ wrote, "Rest remains the sovereign remedy for tuberculosis. Rest alone has returned thousands of consumptives to productive life." This pronouncement has served as the underlying tenet upon which all tuberculosis therapy is based. All collapse procedures, minor or major, have been considered simply as adjuncts to rest. Even this hitherto inviolable principle has been attacked recently. Bray⁷ deplors the marked loss of muscular tone and disturbance of the physiologic

processes of the body which follow enforced curtailment of physical activities. Krusen,¹⁶ too, emphasizes the benefits to be derived from graded activity in the management of certain tuberculous patients. Dock,¹⁷ a bitter critic of bed rest, considers it a highly unphysiologic and definitely hazardous form of therapy. During the course of discussion of the use and abuse of bed rest in a Cornell Conference on Therapy, Dock implied that the dangers of strict bed rest in tuberculosis were underestimated. In his series of medical cases 5 per cent of emboli were in tuberculous patients and almost all were fatal. Peck¹⁸ has accepted the current indictment of bed rest as a challenge to phthisiologists to re-evaluate their concepts of this type of therapy. He attempts to answer the question of whether the dangers of bed rest as applied to the tuberculous person are commensurate with the risk which tuberculous patients must take when treated without bed rest. He concludes that bed rest is inherently valuable but only when it is made a distinct medical responsibility warranting constant and critical attention by the physician.

The crucial argument against bed rest in tuberculosis would appear to be the clear demonstration that it is responsible for irreparable physical damage and even loss of life. This has been demonstrated for the postoperative, cardiac and obstetric patient. The principal evil of bed rest in these groups is pulmonary embolism or its precursor, peripheral venous thrombosis. Such has not been adequately demonstrated in

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the case of tuberculosis. The only study in the literature on the incidence of thromboembolic insults in tuberculosis is that of Peck and Willis¹⁹ who reported that of 751 autopsied cases, evidence of pulmonary embolism was obtained in eleven (1.5 per cent). They observed, furthermore, that in only two instances out of 751 autopsies could infarction have contributed to death. They concluded that pulmonary infarction did not appear to be a danger of great consequence to the tuberculous patient treated with bed rest.

In an effort to evaluate the dangers of bed rest in tuberculosis as related to thromboembolism a review of the entire series of autopsies performed at Fitzsimons General Hospital was undertaken. Since 1921, 3,672 postmortem examinations have been performed of which 1,700 were on tuberculous and 1,972 on non-tuberculous subjects. It should be stated at this time that all instances of septic thrombosis and infarction were eliminated from the study.

In the 1,972 cases in which the cause of death was non-tuberculous 148 (7.5 per cent) instances of pulmonary embolism and/or peripheral venous thrombosis were noted. This incidence is somewhat lower than is generally reported and may be a reflection of the rather rigid and understandable restrictions placed on the extent of dissection of extremities at the Fitzsimons General Hospital. Belt²⁰ and Breslich²¹ believed that pulmonary embolism is present in some 10 to 12 per cent of routine postmortem examinations on adults. McCartney,²² basing his data on 25,771 necropsies, noted that embolism or the possibility of embolism (peripheral venous thrombosis) occurred in 10 per cent of cases. It is quite obvious that the figures of Rössle,²³ 27.1 per cent, Putzer,²⁴ 27 per cent, and especially those of Hunter and associates,²⁵ 52.7 per cent, are not comparable inasmuch as they were derived after meticulous dissection of the lower limbs.

In the 1,700 tuberculous cases which came to autopsy, pulmonary embolism and/or peripheral venous thrombosis oc-

curred in thirty-six (2.1 per cent). This is a startlingly low figure and confirms the previous studies of Peck and Willis.¹⁹ It indicates that pulmonary embolic phenomena, or the possibility thereof, occur much less frequently in tuberculosis than in non-tuberculous diseases. Invoking only the autopsy figures of this institution, we find that the incidence of thromboembolism in the tuberculous group was less than one-third of that in the non-tuberculous series. A comparison with the results obtained by Belt, Breslich and McCartney indicates that the incidence of embolic insults and its precursor, venous thrombosis, in tuberculosis was approximately one-fifth of their recorded figures. This discrepancy is brought into even greater relief when the thirty-six cases are subjected to careful analysis. (Table I.)

Six cases developed thromboembolic features within twenty-one days of operation. In each instance death was due to postoperative embolism. The following cases are illustrative:

CASE 7. A thirty-five year old white male, presenting moderately advanced pulmonary disease, suffered severe diarrhea. An ileostomy was performed for irrigation purposes. Evidence of thrombosis of the left femoral vein was detected eighteen days postoperatively. Five days later the patient developed severe pain in the left chest and expired in a few hours. Autopsy revealed thrombosis of the left femoral vein with large infarcted areas in the right and left lower lobes.

CASE 8. A right upper-stage thoracoplasty was performed on a forty-four year old white male. Three days later he suddenly became dyspneic and cyanotic. Death ensued within a few hours. Autopsy revealed a massive embolus to the left pulmonary artery. The source of the embolus was not detected.

In the remaining four cases death followed the operations of thoracoplasty, spinal fusion, pneumonolysis and phrenemphraxis.

In four instances the clinical picture of congestive heart failure was confirmed by autopsy findings. The following case illustrates this group:

TABLE I
SUMMARY OF CASES OF THROMBOEMBOLISM IN TUBERCULOSIS

Case No.	Age	Sex	Color	Extent of Pulmonary Tuberculosis	Conditions Present with Tuberculosis	Duration of Bed Rest	Recent Operation	Venous Thrombosis	Pulmonary Embolism	Diagnosed Clinically	Non-tuberculous Disease	Remarks
1	36	M	W	Far advanced	Laryngitis, enteritis, peritonitis, pericarditis	3 mo.	None	Left iliac vein	None	Yes	Lucite aortitis	Terminal thrombosis
2	24	M	W	Far advanced	Laryngitis, enteritis, perforation of intestinal ulcer, peritonitis, tubercles in liver and spleen	5 mo.	None	Left iliac vein	None	Yes	None	Terminal thrombosis; death due to perforated intestinal ulcer
3	21	M	W	Far advanced	Enteritis, mixed empyema left, with bronchopleural fistula	3 mo.	None	None	Left lower lobe	No	Generalized amyloidosis	Rapid downhill course; terminal infarct
4	22	M	W	Far advanced	Enteritis, tubercles in kidney and liver	24 mo.	None	None	Left main pulmonary artery	No	Fatty liver	Gradual decline, firm thrombus in right auricular appendage which may have been source of embolus
5	43	M	W	Far advanced	Meningitis, epididymitis, laryngitis, tubercles in liver, spleen, kidneys, seminal vesiculitis	7 mo.	None	None	Right lower lobe	No	None	Gradual decline; death due to lymphohematogenous dissemination
6	37	M	W	Far advanced	Laryngitis, enteritis, peritonitis	3 mo.	None	None	Left pulmonary artery	No	None	Gradual decline; entered hospital in terminal state
7	35	M	W	Moderately advanced	Enteritis	6 mo.	Ileostomy 20 days prior to death	Left femoral vein	Right and left lower lobes	Yes	None	Sudden exitus; death due to embolism and should be classified as a postoperative death
8	44	M	W	Far advanced	None	6 mo.	Thoracoplasty 3 days prior to death	None	Left pulmonary artery	Yes	None	Sudden death attributable to embolism and should be classified as a postoperative death
9	33	F	W	Moderately advanced	None	24 mo.	Thoracoplasty 20 days, and phrenicotracheal 1 day prior to death	None	Right and left pulmonary arteries	Yes	None	As in Cases 7 and 8
10	36	M	W	Far advanced	Enteritis, tubercles in spleen and kidneys	22 mo.	Thoracoplasty 4 months prior to death	None	Left pulmonary artery	No	None	Gradual decline; embolus not attributable to operative interference
11	45	M	W	Far advanced	Enteritis, laryngitis, tubercles in liver, spleen, and kidneys	3 wk.	None	Left and right external saphenous veins	None	No	None	Rapid downhill course. Terminal thrombosis
12	32	M	N	Far advanced	Enteritis, laryngitis, tubercles in both adrenals	1 mo.	None	Superior vena cava	Left pulmonary artery	No	Diabetes mellitus, severe	Sudden death due to embolus
13	24	M	W	Far advanced	Enteritis, peritonitis, laryngitis, empyema, tubercles in liver, spleen, and kidneys	4 mo.	None	None	Left lower lobe	No	None	Gradual decline. Terminal infarct.
14	24	M	W	Far advanced	Meningitis, prostatitis, tubercles in liver, spleen, and kidneys	6 mo.	None	Left and right common iliac veins	None	Yes	None	Death due to meningitis. Terminal thrombosis
15	58	M	W	Moderately advanced	None	5 mo.	None	None	Right lower lobe	No	A.S.H.D. * congestive failure	Death due to A.S.H.D. and congestive failure; (heart weighed 540 Gm.); terminal infarct
16	45	M	W	Far advanced	Meningitis	3 mo.	None	None	Left lower lobe	No	None	Rapid decline; death due to meningitis; terminal infarct
17	40	M	W	Moderately advanced	Mediastinal node involvement	2 wk.	None	Superior vena cava	Left lower lobe	Yes	None	Superior vena cava syndrome due to compression by large tuberculous nodes
18	41	M	W	Far advanced	Mixed empyema right, with bronchopleural fistula, enteritis, peritonitis	8 mo.	None	None	Left lower lobe	No	Generalized amyloidosis	Gradual downhill course; terminal infarct

Case No.	Age	Sex	Color	Extent of Pulmonary Tuberculosis	Conditions Present with Tuberculosis	Duration of Bed Rest	Recent Operation	Venous Thrombosis	Pulmonary Embolism	Diagnosed Clinically	Non-tuberculous Disease	Remarks
19	21	M	W	Minimal	Massive involvement of both kidneys, prostate, epididymis, bladder, enteritis	7 mo.	None	Left iliac vein	Right lower lobe	No	None	Gradual decline; terminal embolism
20	24	M	W	Far advanced	Enteritis, mixed empyema left, bronchopleural fistula	2 mo.	None	Left iliac vein	None	No	Right heart hypertrophy	Gradual decline; terminal thrombosis
21	27	F	N	Far advanced	Enteritis, mixed empyema, left, with bronchopleural fistula, pericarditis	2 mo.	None	Left and right iliac veins	None	No	Decubitus ulcers	Rapid downhill course; terminal thrombosis
22	31	F	W	Far advanced	Pericarditis, enteritis	36 mo.	None	None	Left pulmonary artery	No	Cor pulmonale with congestive failure, right ventricle 0.8 cm.	Sudden death due to embolism
23	51	M	W	Far advanced	Meningitis, enteritis	1 mo.	None	Left iliac vein	None	No	Chronic alcoholism, B-complex deficiency	Rapid decline; died in alcoholic delirium
24	21	M	W	Far advanced	Tubercles in liver, spleen, kidneys, thyroid, adrenals	3 mo.	None	Left femoral vein	None	No	None	Lymphohematogenous tuberculosis cause of death
25	64	M	N	Far advanced	None	5 mo.	None	Right popliteal vein	None	No	A.S.H.D.* with congestive failure	Patient died in severe congestive failure
26	47	M	W	Far advanced	Enteritis, laryngitis, rectal fistulas	4 mo.	None	Left and right femoral veins	None	Yes	None	Gradual decline; terminal thrombosis
27	52	M	W	Far advanced	Enteritis, laryngitis	3 mo.	None	Left femoral vein	None	Yes	None	Gradual decline; terminal thrombosis
28	40	M	W	Far advanced	Laryngitis, tubercles in liver and spleen	1 mo.	None	Periprostatic plexus	Left and right pulmonary arteries	No	None	Rapid downhill course; embolism contributed to death
29	52	M	W	Far advanced	Mixed empyema right, with bronchopleural fistula	4 mo.	Thoracotomy days prior to death	Left renal vein	Multiple pulmonary infarcts	No	Generalized amyloidosis	Sudden death due to embolism and should be classified as a post-operative death
30	44	M	W	Far advanced	Mixed empyema, left, with bronchopleural fistula, tubercles in kidneys, liver, spleen, prostatitis	11 mo.	None	Left femoral vein	None	Yes	Cor pulmonale (right ventricle 0.8 cm.) and septal defect	Patient died in congestive failure
31	31	M	N	None	Osteo. of spine, prostatitis, tubercles in kidney, cystitis, transverse myelitis	7 mo.	Drainage of paravertebral abscess 4 months prior to death	None	Multiple lateral infarcts	No	None	Gradual decline; source of embolism not discovered
32	42	M	N	None	Osteo. of spine, prostatitis, epididymitis, tubercles in kidneys	3 mo.	Spinal fusion 1 day prior to death	None	Left pulmonary artery, massive	Yes	None	Sudden death due to embolism and should be classified as postoperative death; source of embolus not discovered
33	32	M	W	Far advanced	Empyema, right, enteritis	18 mo.	None	Periprostatic plexus	None	No	None	Gradual decline; terminal thrombosis
34	25	M	W	Far advanced	Enteritis, empyema, right, tubercles in liver and spleen	6 mo.	None	None	Left lower lobe	No	None	Gradual decline; terminal infarction; source of embolus not discovered
35	31	M	N	Far advanced	Laryngitis	2 mo.	None	Left iliac vein	Right lower lobe	No	None	Sudden death due to embolism
36	27	M	W	Moderately advanced	None	4 mo.	Pneumonolysis 20 days prior to death	Left hypogastric vein	Multiple bilateral infarcts	Yes	None	Sudden death due to embolism and should be classified as a postoperative death

* A.S.H.D. = arteriosclerotic heart disease.

CASE 15. A fifty-eight year old white male, with a history of pulmonary tuberculosis for thirteen years, was admitted to Fitzsimons General Hospital for shortness of breath and swelling of his legs. Physical examination revealed dyspnea, orthopnea, bilateral basal râles, hepatomegaly and marked peripheral edema. Digitalization resulted in considerable improvement during the first three months of hospitalization but thereafter the patient's course was slowly downhill and he died five months after admission. At autopsy the only evidence of tuberculosis was the presence of an obsolete cavity at the left apex with a few satellite fibrotic tubercles in the immediate vicinity. The heart weighed 540 Gm. and exhibited marked myocardial fibrosis with evidence of an old infarct. The coronary arteries showed severe sclerosis and the liver was markedly congested. There was a small infarct in the right lower lobe; no evidence of venous thrombosis was found.

The anatomic diagnoses in the other three cases of this group were: (1) arteriosclerotic heart disease with extensive myocardial fibrosis and coronary sclerosis; (2) chronic cor pulmonale (wall of right ventricle measured 0.8 cm. in thickness; (3) chronic cor pulmonale and congenital heart disease with septal defect (wall of right ventricle measured 0.8 cm. in width).

Inasmuch as this study is concerned only with thromboembolism in its relation to the use of bed rest in tuberculosis, the complicating features of the postoperative state and congestive heart failure are obvious. If these cases are withdrawn from the series, a total of twenty-six remain and the corrected figure for incidence is lowered to 1.5 per cent. A further analysis reveals that of the twenty-six cases thromboembolism occurred as a terminal manifestation in twenty-two and in no way was related to the cause of death. In three cases the cause of death was a pulmonary embolic accident.

The remaining case was that of a forty year old white male who presented a picture of superior vena cava obstruction. Dyspnea was the first symptom and was followed in a year by the appearance of dilated superficial veins over the trunk and upper ex-

tremities. Edema of the upper extremities supervened two years after the onset of the original symptom; edema of the lower extremities and death soon followed. Autopsy revealed fibrocaceous tuberculosis of the left upper lobe with a large, tumor-like, tuberculous mediastinal mass encircling and compressing the superior vena cava and producing thrombosis. A large infarct was found in the left lower lobe. This case, too, bears no direct relationship to the problem under discussion inasmuch as the patient was ambulatory during the first twenty months of his illness. In addition the thrombosis was the direct result of the disease process in which massive tuberculous mediastinal nodes compromised the lumen of the superior vena cava and actually invaded the wall of the vessel. As a result two factors commonly associated with the pathogenesis of thrombosis came into play, namely, damage to the wall of the vein and slowing of the blood stream. Nevertheless, the case is included in the series as similar cases occurred in the non-tuberculous group and are represented in the figures of that group.

The average age of the group is 36.1 years; if the postoperative and cardiac cases are excluded, the average age is 33.5 years. This presents a marked contrast to figures previously published. Allen, Linton and Donaldson²⁶ found that 81 per cent of their series of 202 patients with thromboembolism were over forty. Barker and his associates²⁷ in an extensive statistical survey of postoperative thromboembolism noted that the majority occur between the ages of fifty and sixty-nine. Hermann²⁸ observed that the disturbance is rare in patients under thirty. In the present series of thirty-six cases however, eleven (30.5 per cent) occurred between the ages of twenty and twenty-nine, and twenty-one (58.3 per cent) occurred below the age of forty. The wide difference in age incidence is accentuated further when comparison is made with the Fitzsimons non-tuberculous group in which the average age was 51.1 years and only 17.5 per cent of cases occurred below the age of forty. (Table II.)

Attention has been drawn repeatedly to the difficulty with which the source of embolism is demonstrated despite diligent postmortem search. Barker et al.²⁹ noted that of 897 cases of pulmonary embolism clinical or autopsy evidence of venous thrombosis could not be obtained in 45.2 per cent. Of the thirty-six cases of thromboembolism in tuberculous subjects there were twenty-three instances of pulmonary embolism. Autopsy evidence of venous thrombosis was lacking in fifteen (65.2 per cent). Of the 148 instances of thromboembolism in the comparable non-tuberculous group of autopsies, 123 presented pulmonary embolic phenomena. Postmortem evidence of venous thrombosis in this series was lacking in 112 cases (91.1 per cent). The almost complete failure to locate the source of the embolus in the latter group of cases may be attributed to (1) the previously mentioned reluctance to perform extensive leg dissection at this institution, and (2) the large number of cardiac patients which make up this series (Table III) and, more particularly, to the frequency with which cardiac mural thrombi were observed in this type of pa-

affirmed by the fact that the autopsies in both groups were performed under the same hospital regulations and by the same individuals. The significant conclusion from this observation would appear to be that in patients with congestive heart failure cardiac

TABLE II
AGE DISTRIBUTION

Age in Years	Tuberculous		Non-tuberculous	
	No. Cases	Per Cent	No. Cases	Per Cent
10-19	0	0	3	2
20-29	11	30.5	14	9.5
30-39	10	27.8	9	6.1
40-49	10	27.8	42	28.3
50-59	4	11.2	44	29.7
60-69	1	2.7	21	14.2
70-79	0	0	8	5.4
80-89	0	0	5	3.4
90-99	0	0	1	0.7
100-109	0	0	1	0.7
Total	36	100	148	100
Average Age	36.16		51.04	

TABLE III
INCIDENCE OF PREDISPOSING CONDITIONS

Type of Patients	Total No. Cases of Thrombo-embolism	Predisposing Conditions								Terminal Physical State		None	
		Cardiac Disease		Postopera- tive State		Carcinoma		Fractures					
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Tuberculous.....	36	4	11.1	6	16.6	0	0	0	0	22	61.1	4	11.1
Non-tuberculous.....	148	70	47.3	24	16.2	26	17.6	8	5.4	18	12.1	2	1.4

tient. It is generally agreed that in cardiac patients mural thrombi may serve as an important source of embolization.³⁰ This is suggested by the wide difference in the figures of the tuberculous and non-tuberculous groups. The validity of this discrepancy (91.1 per cent as opposed to 65.2 per cent) is

mural thrombi are a more important source of potentially lethal emboli than the venous channels of the extremities.

In those instances in which evidence of venous thrombosis is detected, its location is usually in the lower extremities. In the thirty-six instances of thromboembolism

among tuberculous subjects the site of thrombosis, with or without embolism, is summarized in Table IV. The predilection of thrombosis for the lower extremities is evidenced by the fact that 76 per cent occurred at that site. In the non-tuberculous

TABLE IV
LOCATION OF THROMBOSIS

Site	Tuberculous Cases		Non-tuberculous Cases	
	No.	Per Cent	No.	Per Cent
Left iliac vein	7	28	6	14.7
Left femoral vein	5	20	3	7.3
Periprostatic plexus	2	8	5	12.3
Superior vena cava	2	8	1	2.4
Left renal vein	1	4	0	0
Left hypogastric vein	1	4	0	0
Left external saphenous	1	4	0	0
Right external saphenous	1	4	3	7.3
Right femoral vein	1	4	1	2.4
Right iliac vein	1	4	4	9.7
Left common iliac vein	1	4	6	14.7
Right common iliac vein	1	4	6	14.7
Right popliteal vein	1	4	0	0
Portal vein	0	0	2	4.9
Left spermatic vein	0	0	1	2.4
Corpora cavernosa	0	0	1	2.4
Right median basilic vein	0	0	1	2.4
Bilateral axillary and brachial veins	0	0	1	2.4
Total	25	100	41	100

group in which thrombosis occurred in 70.8 per cent the same preference for the lower extremities is noted. Although the leg veins are implicated in the great majority of cases, we cannot concur with Allen's³¹ opinion that 95 per cent of thromboses are located in the lower limbs. In 108 cases of pulmonary embolism studied by Sagall et al.³² the source of the embolism was presumably from thrombosis of leg veins in ninety (83.3 per cent). That the source of embolization in a significant number of cases is located in the pelvic and abdominal veins is well demonstrated in Table III.

Homans³³ as well as Hampton et al.³⁴ have discussed the obscure sources which may be responsible for pulmonary embolism. The latter group cited one instance of thrombosis of the periprostatic venous plexus. A glance at Table III reveals that venous thrombosis in this location occurred twice in the tuberculous series and on five occasions in the non-tuberculous series. It is of interest that in the two tuberculous cases the prostate was not involved in the tuberculous process. Hampton's cases occurred in Army personnel and he emphasized the possible rôle of exertion and vigorous exercise in producing embolism from silent sources. This belief was supported by the fact that similar cases were rarely encountered in civilian life in which the type of exercise is usually much less arduous. Both instances of periprostatic venous thrombosis in the tuberculous series occurred in far advanced cases with serious extrapulmonary complications. Similarly, the five instances of periprostatic venous thrombosis in the non-tuberculous series occurred in cases of acute myelogenous leukemia, lymphosarcoma of the stomach, fracture of the fifth cervical vertebra with contusion of the spinal cord, bronchogenic carcinoma and decompensated syphilitic heart disease, respectively. In other words, all seven patients had been bedridden for considerable periods of time. In only one instance did pulmonary embolism occur. This observation lends support to the belief of Hampton et al.³⁴ that vigorous exercise plays an important rôle in the production of emboli from obscure sources. Two additional obscure sites of thrombosis were located in (1) the left spermatic vein occurring in a case of extensive fatal burns, and (2) corpora cavernosa of the penis complicating a case of chronic myelogenous leukemia.

In view of Dock's³⁵ indictment of bed rest in the production of thrombosis and the statement of Hunter and associates³⁶ that the common denominator in most cases of phlebothrombosis is confinement to bed, it would follow that there should be a direct correlation between the duration of bed

rest and the incidence of thromboembolism. A glance at Table 1 indicates that no such correlation exists. The duration of bed rest varied from two weeks to thirty-six months. The average period of bed rest for those patients in the third decade was 6.3 months, for those in the fourth decade 10.3 months and for those dying in the fifth decade 5.4 months.

COMMENT

The relatively low incidence of thromboembolism in tuberculous patients appears to be established by this study. The reasons for this comparative insusceptibility are not clear. The factors commonly associated with the pathogenesis of thrombosis are (1) alterations in the wall of the vein, (2) alterations in the blood constituents and (3) slowing of the blood stream. No intimal changes have been described in tuberculosis except in those relatively infrequent instances in which the disease process actually involves the wall of the vein as exemplified by Case 17. The suggestion that tissue damage is produced by prolonged pressure of the extremity on the bed has been advanced by Dock³⁵ and Frykholm³⁷ and circumstantial evidence has been offered by Simpson³⁸ but no satisfactory objective proof of such has been forthcoming.

Increase in the number of platelets as well as an increase in their agglutinability have been described in postoperative patients.^{39,40,41} Aschoff⁴² attributed an important part to these factors in the pathogenesis of thrombosis. Thrombocytosis has not been described in the tuberculous patient treated with bed rest.

Hyperprothrombinemia has been described by Shapiro⁴³ as being a frequent accompaniment of thromboembolism developing after surgery. However, Cotlove and Vorzimer⁴⁴ could find no evidence of increased prothrombin activity as a result of bed rest, nor was it influenced by the presence of congestive heart failure. The administration of digitalis has also been shown to have little or no effect on the prothrombin time and coagulability of

blood.^{44,45} Although the studies on prothrombin activity in tuberculosis are not many, they indicate that hypoprothrombinemia rather than prothrombin hyperactivity exists in an appreciable number of cases.

One of the earliest reports in the literature dealing with prothrombin activity in tuberculosis is that by Scoz, Bergami and Castaldi⁴⁶ which, together with the work of subsequent investigators,⁴⁷⁻⁵¹ indicates that a prothrombin deficiency occurs in about one-third of tuberculous patients. The deficiency manifests itself especially in those patients with fever and other constitutional symptoms. In this group prothrombin deficiency may occur in 50 per cent of cases. This immediately raises the problem of whether a significant degree of hypoprothrombinemia prohibits the occurrence of thrombosis. Some patients with advanced cirrhosis of the liver and with ulcerative colitis exhibit a severe hypoprothrombinemia in spite of which thrombosis develops.⁵² While prothrombin is an important factor in the process of clotting, this mechanism may still operate in the presence of diminished quantities of prothrombin. The importance of hypoprothrombinemia as the responsible agent for the low incidence of thromboembolism in tuberculosis remains to be determined. No reports on Bancroft's plasma clotting index¹⁴ in relation to bed rest in tuberculosis have appeared in the literature. As this test is really a measure of prothrombin activity, further studies along this line are indicated.

Another factor which may operate to a greater degree than has previously been considered is the influence which altered blood volume may exert on the clotting mechanism. In an excellent study on the effect of three weeks' bed rest on the blood volume of five normal individuals Taylor and his associates⁵³ observed an average loss in blood volume of 572 ml. (9.3 per cent). This was almost entirely accounted for by a contraction of the plasma volume of 518 ml. (15.5 per cent). An additional study revealed that the blood volume change after

surgical repair of an inguinal hernia and three weeks' bed rest in one man did not differ significantly from the changes observed in the same man after bed rest alone. This significant diminution in plasma volume implies a relative increase in the formed elements of the blood as well as an increase in the blood viscosity. Here then is a factor which has not been studied sufficiently.

If a three-week period of bed rest results in a significant lowering of blood and plasma volume and if such a phenomenon plays an important rôle in the production of thrombosis, it follows that thrombosis should occur more frequently in tuberculous patients treated with bed rest than in any other group of individuals. It has already been demonstrated that the opposite is the case. The reason for this may lie in the relatively large quantities of fluids taken by the tuberculous patient. The majority of patients at the Fitzsimons General Hospital drink about a quart of milk daily in addition to their extra fluid nourishments which are given three times a day. There is little doubt that the fluid consumption of the tuberculous individual is considerably higher than the normal healthy person, and much more so than the cardiac or postoperative patient.

Of all the factors involved in the production of venous thrombosis, circulatory stasis has been given greatest emphasis. Therefore, bed rest with its resultant slowing of the blood stream has been severely implicated. The marked influence of circulatory stasis on thrombosis was quickly recognized by Rowntree, Shionoya and Johnson.⁵⁴ These workers employed an extracorporeal cannula loop, the cannula being inserted into the carotid artery and the jugular vein of rabbits. They noted that anything which tended to retard circulation would hasten the process of thrombosis.

Smith and Allen⁵⁵ observed that 82 per cent of patients showed significant slowing of circulation in the foot to the carotid sinus pathway after operation. They believed that circulatory stasis plays a very important rôle in the production of postoperative thrombosis. This was also emphasized ex-

perimentally by Rabinovitch and Pines⁵⁶ who found it necessary to add stasis (by partial ligation of the vein) to the intimal damage produced by stretching the vein to insure thrombosis. Similarly, Moscs⁵⁷ found stasis a prerequisite for the consistent production of occluding thrombosis by the insertion of intravascular foreign bodies.

Frimann-Dahl⁸ determined the emptying time of the saphenous vein before and after operation and in patients who had been bedridden for long periods of time. He injected a small amount of opaque substance into the saphenous vein and watched its disappearance under fluoroscopy. Normally this took from five to thirty seconds. Bedridden patients, unless they had toxic thyroids, showed a retardation of one to two minutes; whereas after major abdominal operations the emptying time was prolonged from three and one-half to four minutes. In some cases the venous flow was practically stagnant up to the time the patient first became ambulatory. Frimann-Dahl also followed the respiratory excursions of the diaphragm before and several times after operation in twenty cases. He observed a marked reduction in the movements of the diaphragm following operation. Nissen and Wustmann⁵⁹ determined the emptying time of the inferior vena cava before and after phrenicotomy and found that the time it took the contrast medium to disappear doubled after the diaphragm was paralyzed.

It has been demonstrated⁶⁰ that the reflex inhibition of respiration will temporarily obstruct the return flow of blood to the heart. Potts and Smith⁶¹ noted that the blood flow from the inferior vena cava dropped almost to zero following over-inflation of the dog's lungs. When the obstruction in the pulmonary bed was released, a prompt and marked rise occurred in circulation. There can be little doubt that free and unhampered movement of the thorax plays an important rôle in promoting the circulation of blood from the peripheral to the thoracic veins. Indeed, Ochsner⁶² insists on the routine use of deep

breathing exercises postoperatively as a prophylactic measure against venous thrombosis. Although the mechanics of respiration in many tuberculous patients are hampered by collapse measures, this is probably more than offset by their vigorous coughing. Even the patient with minimal disease raises all secretions from his tracheobronchial tree because of his understanding of the benefits of proper drainage and the dangers of swallowed sputum. The act of coughing is followed by deep inspiration; repetition of this act several times daily with its increase in the negativity of intrathoracic pressure furthers the flow of blood from the periphery to the heart.

The importance of cough and its subsequent deep inspiration may be reflected in the low incidence of pulmonary embolism following chest surgery. During the four-year period from November, 1942, to November, 1946, 2,247 chest surgical procedures were performed on tuberculous patients at the Fitzsimons General Hospital. In only one instance did pulmonary embolism occur. It is a routine procedure on the Chest Surgical Service following operation to have the patient cough vigorously every two hours as soon as consciousness has been regained.⁶³ While this procedure has as its primary aims the rapid re-expansion of lung and the proper cleansing of the tracheobronchial tree, it serves a secondary purpose in the maintenance of adequate blood flow from the periphery to the thorax.

Much attention has been focused on the dangers of the Valsalva experiment (forced expiration against a closed glottis) in the presence of venous thrombosis.⁶⁴ However, scant notice has been paid to the converse experiment of Mueller (forced inspiration with a closed glottis), the powerful suction effect of which may produce a fall of 50 mm. of water on the venous pressure of a peripheral vein.⁶⁵ The Mueller procedure is probably used by most tuberculous patients immediately upon awakening. Although the glottis is not completely closed during this act, it certainly is narrowed during the inspiratory phase necessary to suction secre-

tions down from the nasopharynx and sinuses.

An additional factor in the etiology of thrombosis has recently arisen as a result of the work of Finland and his co-workers.⁶⁶ These observers noted that a number of patients with primary atypical pneumonia with high titers of cold hemagglutinins developed phlebothrombosis and pulmonary emboli. Although the presence of cold hemagglutinins in low titer is frequently found in other respiratory infections, large amounts are rarely observed except in primary atypical pneumonia. While the development of thrombosis in this disease may depend, in part, on the presence of cold hemagglutinins in high titer, it is unlikely that the latter phenomenon plays an outstanding rôle in the overall picture of thrombosis. Certainly its importance in tuberculosis is negligible. Siffert and Krautman⁶⁷ observed that of eighty-two tuberculous patients, seventeen showed the presence of iso-agglutinins in 1:4 dilution. However, none showed a titer high enough to be significant.

It is obvious from this review of the etiologic factors in the production of thrombosis that no satisfactory reason has been found to explain the low incidence of thromboembolism in tuberculosis. Although low prothrombin, increased fluid intake, frequent cough and indulgence in the Mueller experiment may individually contribute in some measure to the low incidence, the extent of these contributions is pure conjecture. The only objective difference between the tuberculous and non-tuberculous groups is that of age. Tuberculous patients at the Fitzsimons General Hospital are naturally drawn from military personnel on active duty; the great majority are in their third and fourth decades. It is quite possible that figures from a civilian tuberculosis institution, where a larger proportion of patients are in the older age group, would show an incidence of thromboembolism more comparable with that reported for non-tuberculous patients. However, the figures reported by Peck and Willis¹⁹ from

Maybury Sanatorium that evidence of pulmonary embolism was obtained in only eleven (1.5 per cent) of 751 autopsied cases suggests that civilian experience is similar to that reported in this paper.

From this study, two significant conclusions may be drawn: (1) Thromboembolism is not a threat to the life of the tuberculous individual and (2) it follows as a natural corollary that the dangers of bed rest in tuberculosis as related to thromboembolism are minimal and cannot be used as a basis for argument against this therapeutic agent. A clear demonstration of the value of strict bed rest in the treatment of tuberculosis has been presented by Amberson.⁶⁸ Until a study comparable to his in number of patients and length of follow-up observations is presented, and in which it is definitely shown that equally good results are obtained without the use of strict bed rest, the latter measure should remain the foundation of tuberculosis therapy.

SUMMARY

1. The danger of thromboembolism has been used by some internists and phthisiologists as an argument against the application of strict bed rest in the treatment of tuberculosis.

2. A review of 3,672 autopsies at Fitzsimons General Hospital of which 1,700 were on tuberculous subjects reveals an uncorrected incidence of thromboembolism in the tuberculous group of 2.1 per cent and a corrected incidence of 1.5 per cent. This incidence is less than one-fifth of the figures reported in the literature for non-tuberculous diseases. In only three cases could the cause of death be ascribed to a pulmonary embolic accident.

3. The suggestion is presented that in cardiac patients mural thrombi may be a more important source of emboli than the peripheral venous channels.

4. The etiologic factors in the production of thrombosis are discussed. Further studies on prothrombin content, blood volume and peripheral blood flow in relation to tuber-

culosis, bed rest and thromboembolism are indicated.

5. Thromboembolism does not constitute a significant threat to the life of the tuberculous individual who is being treated with strict bed rest.

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Paroxysmal Hypertension Associated with Tabes Dorsalis*

Report of Three Cases

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THE syndrome of paroxysmal hypertension is characterized by sudden, spontaneous rises in arterial blood pressure; between paroxysms the pressure is normal or only slightly elevated. The periods of hypertension may or may not be associated with symptoms. In the minds of many physicians paroxysmal hypertension is synonymous with pheochromocytoma, a tumor of the adrenal medulla.^{1,2} There are, however, several other conditions which may be accompanied by similar wide variations in arterial pressure. They include eclampsia, lead colic, the abdominal angina of Nothnagel, cerebral tumor and tabes dorsalis.^{3,4 5}

The occurrence of paroxysmal hypertension in patients with tabes dorsalis seems to have received little attention in recent years. Although there are a few brief references to this association in various textbooks and monographs,⁵⁻⁸ we have not been able to find any clinical studies of this condition in the literature since 1911.

In 1903 Pal made the observation that occasionally the gastric crises of tabes were accompanied by sudden rises in arterial pressure.⁹ He attempted to differentiate between the "grand gastric crisis" of tabes, which consisted of hypertension, pain, nausea and vomiting, and the milder types of abdominal and visceral episodes. In 1905 he published a monograph on vascular crises¹⁰ which contained observations

on eighteen patients with tabetic gastric crises. Twelve of these eighteen patients had marked rises in blood pressure accompanying the crises. Pal postulated that the hypertension was the precipitating factor in these cases. According to his theory the first event is a sudden splanchnic arteriolar spasm caused by a reflex from irritation of the dorsal root fibers. This is followed by dilatation of the vessel segments proximal to the constriction which stretches the nerve plexuses in the vessel walls and causes the agonizing abdominal pain. Pal supported this theory by the observation that in other types of severe abdominal pain (excepting lead colic), such as biliary or renal colic, there was no remarkable rise in blood pressure. He also noted that reduction of blood pressure by means of amyl nitrite, warm baths, and in one patient by an attack of paroxysmal tachycardia, invariably relieved the pain until the pressure again mounted. He pointed out that morphine relieved the pain but had no effect on the hypertension. In all of the patients with lightning pains in the legs whom he observed, the blood pressure remained normal or dropped slightly.

In 1908 Heitz and Norero reported attempts to confirm Pal's observations.¹¹ Taking blood pressure readings four times daily, they followed six patients with tabes for a three-month period. Four of their patients were found to have the grand

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gastric crises described by Pal but in these cases the onset of the abdominal pain and nausea invariably preceded the rise in blood pressure. They concluded that although the vasoconstrictive phenomenon was associated with the grand gastric crises, it was secondary to the pain. They attributed the pain to irritation of the posterior spinal roots, with accompanying motor reflexes (vomiting, constipation) and vasoconstrictive reflexes (hypertension).

In 1910 Barker described a patient with tabes who had severe gastric crises accompanied by marked rises in blood pressure.¹² In this patient the inhalation of amyl nitrite caused the blood pressure to fall to normal, with temporary amelioration of the symptoms of the gastric crisis. In 1911 Iozefovich and Lifshits reported a patient in whom gastric crises were associated with hypertension and agreed in general with Pal's conclusions.¹³ In the same year Claude and Cotoni described another patient in whom the same parallelism between variations in blood pressure and gastric symptoms was observed.¹⁴ They noted on one occasion that an injection of epinephrine precipitated a typical gastric crisis with hypertension which lasted six days. Measures which lowered the blood pressure also afforded temporary relief of pain and nausea in this patient, and Claude and Cotoni concluded that Pal was probably correct in placing the pain and nausea secondary to the hypertension.

In 1916 Nuzum reviewed the records of 1,000 patients with tabes from the Cook County Hospital.¹⁵ Referring to Barker, Nuzum simply states that blood pressure may be elevated during gastric crises but there is no mention of it in his own cases.

In a report of three cases of tabetic gastric crisis in which relief of symptoms had been obtained by neurosurgical procedures, Shawe in 1921 described one patient in whom a gastric crisis with hypertension was precipitated by the subcutaneous injection of epinephrine.¹⁶ This crisis lasted forty-eight hours during which relief of symptoms was afforded by inhalation of amyl nitrite.

Guiraud and Boittelle¹⁷ have recently reported a case of taboparesis complicated by aortic insufficiency and hypertension which was associated with epileptiform seizures, transient aphasia and hemiplegia. During these episodes the patient's blood pressure was sometimes too high to be recorded. There is no mention of gastric symptoms. Although this may represent an example of the paroxysmal hypertension of tabes, the presence of pre-existing hypertension makes it difficult to be certain.

The purpose of the present article is to report three additional cases of paroxysmal hypertension associated with tabes dorsalis. It seems important that this association be appreciated not only in connection with the management of tabes dorsalis but especially to avoid unnecessary surgical exploration of the adrenals.

CASE REPORTS

CASE 1. H. M. S., a fifty-one year old white man, was admitted to Grady Hospital on August 3, 1945, complaining of attacks of nausea and vomiting. Since 1935 he had had attacks of vomiting associated with palpitation, weakness and profuse sweating but unaccompanied by abdominal pain, diarrhea or fever. These episodes had become increasingly frequent and severe in the preceding ten months. They often lasted from two to seven days and, on one occasion, the patient remained in bed for as long as three weeks. Although barbiturates afforded temporary relief, atropine and other belladonna derivatives had always aggravated his nausea and palpitation. The patient stated that his blood pressure had been normal until 1935. Since then he had been told that his blood pressure was usually over 200 during the periods of vomiting and on several occasions it was as high as 260 or 280. Between attacks it had ranged from 115 to 140. During the ten years prior to admission the patient had had four episodes of convulsions followed by unconsciousness, and he maintained that these were caused by laxatives given during attacks of vomiting. For three years he had noticed that his gait had become progressively unsteady and he had experienced attacks of severe, spontaneous, burning pain over the left anterior thigh. For several years he had had increasing nocturia and dribbling in-

continence of urine. He had been catheterized on several occasions for urinary retention.

The patient stated that in 1918 he had several small penile lesions which healed promptly after one intravenous injection of salvarsan. There were no other symptoms suggestive of early syphilis. In 1942 his Kahn test was positive and in 1943 he received weekly injections of tryparamide for a period of ten months. In January, 1945, he was given twenty-four hours of fever therapy in a hypertherm at another hospital.

On admission the chief findings on physical examination were as follows: Blood pressure was 138/80. The pupils were miotic and did not react to light but the accommodation reflex was normal. The visual fields were normal and the ocular fundi showed normal discs, with mild arteriosclerotic changes but without hemorrhages or exudates. The heart and abdomen were normal. The deep tendon reflexes were hypoactive and the ankle jerks were absent. The Romberg test was questionably positive. Position and vibratory sensations in the lower extremities were normal. There was no postural hypotension.

Kidney function as measured by urinalysis, phenolsulphonphthalein excretion, non-protein nitrogen and concentrating ability was normal. Blood glucose during an attack was 99 mg. per cent. The result of the Kahn test was doubtful. The spinal fluid contained 2 lymphocytes per cu. mm., 37 mg. per cent protein and a 4 plus Wassermann with 1 ml. of fluid.

On the second hospital day an attack of hypertension, nausea and vomiting was induced at the suggestion of the patient by giving him a laxative containing cascara. Six hours after ingestion of the drug the patient became pale, perspired profusely and complained continuously of nausea and palpitation but not of pain. His blood pressure rose to 260/170. The pupils became widely dilated but did not react to light. No change was noted in the fundal vessels nor was there any change in heart sounds or pulse rate. The intravenous administration of sodium amytal by slow infusion alleviated his discomfort and the symptoms subsided after three days.

It was thought that the patient had a pheochromocytoma and he was transferred to the Urologic Service. Although attempts to visualize an adrenal tumor by x-ray were inconclusive, bilateral adrenal exploration was done; no tumor was found. Tissue was removed from each adrenal gland and was found to be normal. The

patient recovered uneventfully from the operation but continued to have attacks of hypertension, nausea and vomiting. (Fig. 1.) A histamine test for pheochromocytoma was negative.¹⁸ The patient began to lose weight and appeared to be failing progressively. It was decided to treat

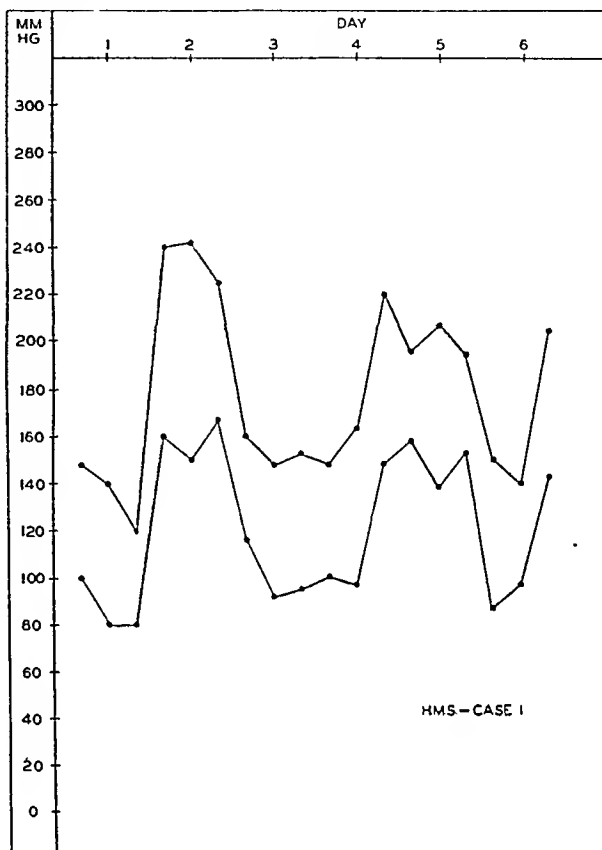


FIG. 1. Blood pressure curve in Case 1 for six days. During this period the patient received no medication and except for one episode of nausea and palpitation on the second day was asymptomatic.

his neurosyphilis with penicillin and he was given 3 million units of sodium penicillin over a period of fifteen days. Shortly thereafter he began to gain weight and the attacks occurred less frequently. When discharged from the hospital on February 16, 1946, he had gained 28 pounds. The patient subsequently was able to return to work as a carpenter and did not return for follow-up examination. When last heard from ten months after leaving the hospital, he reported he had had no further attacks.

CASE II. M.H.M., a thirty-seven year old white man, was admitted to the Surgical Division of Emory University Hospital on October 8, 1946, for bronchoscopy because of an episode of hemoptysis three months previously. Roentgenograms of the chest and routine laboratory studies in the Out-patient Clinic

were normal and his blood pressure was recorded as 120/80 and 114/82. At the time of admission to the hospital, however, his blood pressure was 300/190 and he was transferred to the Medical Service for study.

The patient had never been told previously

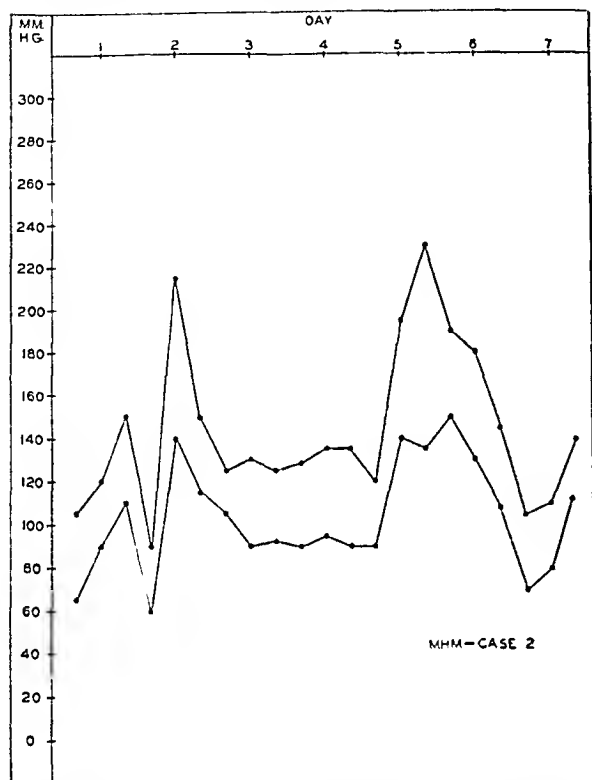


FIG. 2. Blood pressure curve for one week in Case II. The patient received no medication and was asymptomatic throughout this period.

that he had high blood pressure. For about two years he had had what he described as "flying pains" in his legs. These were sharp and lancinating, radiating from thighs to heels and occurring mostly at night. He had also noted increasing nervousness, occasional episodes of blurred vision and dull frontal headache. There had been no symptoms of cardiac decompensation and no symptoms referable to gastrointestinal or urinary tracts. In 1931 the patient had a painless penile ulcer which was diagnosed as a chancre. He was treated sporadically for three years with approximately eighteen arsenical and twenty-four bismuth injections. Repeated serologic tests for syphilis thereafter had been negative. He had never had a spinal fluid examination.

Physical examination on admission revealed unequal pupils, the right being larger than the left. The right pupil reacted sluggishly to light,

the left not at all. Reaction on accommodation was normal. The ocular fundi, heart and abdomen were normal. The Romberg test was negative but knee and ankle jerks were absent. There was no evidence of postural hypotension.

Kidney function as tested by urinalysis, phenolsulphonphthalein excretion, non-protein nitrogen and concentrating ability was normal. The Kahn test was negative. Examination of the spinal fluid revealed 65 lymphocytes per cu. mm., 72 mg. per cent protein and positive Kahn and Kolmer reactions. Skull films and pyelograms were normal.

On the day after admission the patient's blood pressure dropped to 128/80 but repeated examinations showed a variation from 90/55 to 230/135. (Fig. 2.) At no time did the patient have any symptoms associated with these variations in blood pressure. Attempts were made to induce paroxysms of hypertension, but the administration of laxatives, intravenous injection of typhoid vaccine, subcutaneous injection of 1 mg. of epinephrine and brisk exercise all failed to raise the pressure more than momentarily. A cold pressor test gave negative results as did the intravenous injection of histamine, hyperventilation and massage of the kidney areas.

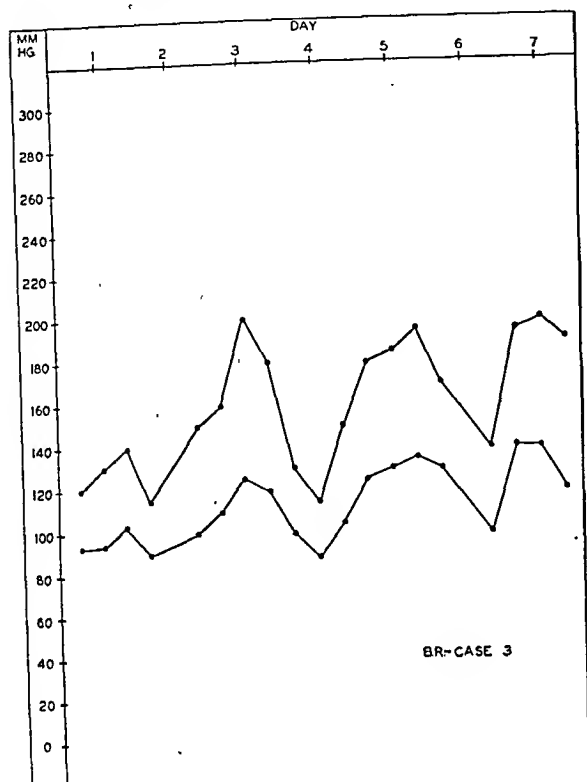
The patient was treated with 6 million units of sodium penicillin over a period of thirteen days and discharged on November 15, 1946. He returned on January 6, 1947, at which time he reported that he had had no more lightning pains and that his nervousness was much improved. His blood pressure, however, was 196/140 on that day.

CASE III. B. R., a forty-two year old white woman, was admitted to Grady Hospital in December, 1946, with the diagnosis of a bleeding marginal peptic ulcer. Three days prior to admission the patient developed epigastric distress and nausea followed by hematemesis and melena. Eight years previously she had had a posterior gastroenterostomy for a duodenal ulcer with obstruction and bleeding.

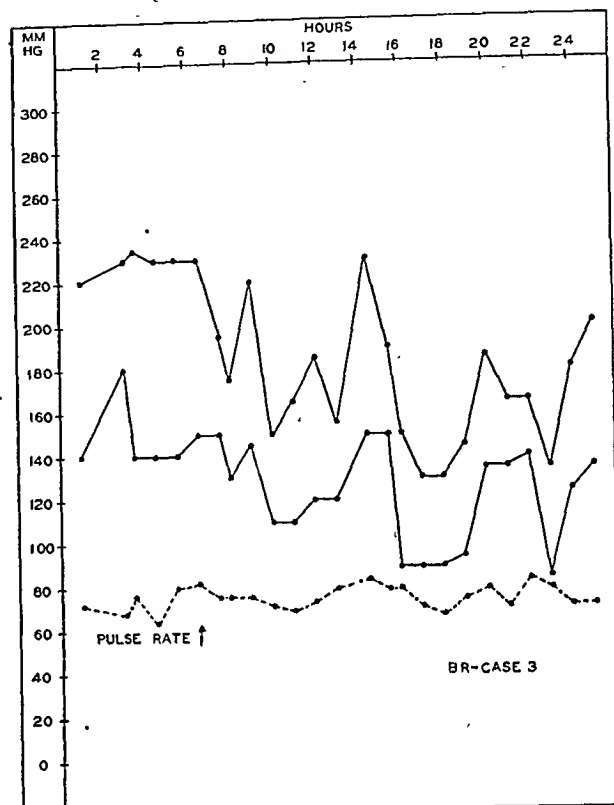
In 1923 the patient was found to have a positive serologic test for syphilis and was given antisyphilitic therapy for six months. Following this treatment her serologic test became negative and she was dismissed as cured. In 1938 she began to have attacks of severe shooting pain in her lower extremities. She also developed urinary frequency and involuntary micturition.

The patient had known for six years that her blood pressure was occasionally elevated although most of the time it was normal. In 1944 she was told by her physician that she had menopausal hypertension and she was given numerous injections of "ovarian extract" with-

on accommodation. Knee jerks were hypoactive, ankle jerks were absent and the Romberg test was positive. There was no postural hypotension. There was no cardiac enlargement and no evidence of vascular disease on ophthalmoscopic examination.



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FIG. 3. Blood pressure curve for one week in Case III. The patient received no medication and was asymptomatic throughout this period.

FIG. 4. Blood pressure record for twenty-four hours after operation (subtotal gastrectomy) in the third patient. Note that the variations in pressure were accompanied by no changes in pulse rate. There was no change in the patient's clinical condition with these variations.

out effect. The patient had been examined in the Out-patient Clinic at Grady Hospital with varying minor complaints since 1934 and the following blood pressures had been recorded: 130/84, 165/120, 200/140, 170/110, 110/70, 140/90, 126/90, 150/100 and 140/96. Although her hypertension was occasionally accompanied by lightning pains, there was usually no association noted. The serologic test for syphilis was negative in 1935, 1938 and 1944. At no time had she had any symptoms suggestive of a tabetic gastric crisis. Her duodenal ulcer was asymptomatic most of the time.

Shortly after entering the hospital the patient began to complain of lancinating leg pains. Neurologic examination revealed miotic pupils which were fixed to light but reacted normally

Kidney function as tested by phenolsulphonphthalein excretion, urinalysis, intravenous pyelograms and concentrating ability was normal. Roentgenographic examination of the skull was normal. The Kahn test was negative. Spinal fluid examination revealed no cells, normal protein and a 4 plus Wassermann with 1 ml. of fluid. The patient was treated with 4 million units of penicillin over a period of ten days. Her blood pressure was recorded at regular intervals during this time and showed variations from 115/85 to 240/150. (Fig. 3.) There was no apparent change following penicillin. On January 21, 1947, a subtotal gastric resection was performed. The post-operative course was smooth except for wide variations in her blood pressure. (Fig. 4.)

Subsequent to operation it was found that a cold pressor test, exercise, subcutaneous epinephrine and hyperventilation did not influence the blood pressure. The intravenous injection of histamine also failed to precipitate a paroxysm of hypertension. She was discharged on February 15, 1947, asymptomatic except for rare attacks of lightning pains.

COMMENT

It seems important to recognize that tabes dorsalis can cause paroxysmal hypertension. Unfamiliarity with this association led to a needless surgical exploration for a pheochromocytoma in the first case presented here.

The previous reports of this syndrome have stressed the association of hypertension with gastric crises. Gastric crises were present in only one of our patients, and in this instance the attacks consisted only of nausea and vomiting unaccompanied by pain. In the second patient the hypertension was entirely asymptomatic. In the third patient the paroxysms of high blood pressure were not accompanied by symptoms except for occasional association with lightning pains.

Although penicillin therapy appeared to have a beneficial effect on the hypertensive crises in the first patient in this series, there was no evidence that it was effective in the other two patients.

We were unable to find any certain means of precipitating hypertension in these patients. The histamine test for pheochromocytoma was uniformly negative. The production of gastric crises in the first patient with the use of laxatives is of interest and has been noted previously.⁶ Because of this lack of a controlled trigger mechanism, it was not possible to carry out satisfactory studies of the circulatory changes associated with the rises in blood pressure. It would be of interest to determine whether an elevation in right ventricular pressure accompanied the attacks since this might indicate an abnormal epinephrine mechanism as an etiologic factor.¹⁹ For the present we can only attribute the attacks to some disturbance of autonomic function.

Similar attacks of paroxysmal hypertension have been observed in patients with paraplegia who develop mass sympathetic crises.²⁰

The present observations indicate that hypertensive crises in patients with tabes are not associated only with gastric crises but may occur without other symptoms. This leads us to believe that paroxysmal hypertension is simply one of the disturbances of the autonomic nervous system that may occur in tabes dorsalis.

CONCLUSIONS

Three patients with paroxysmal hypertension, associated with tabes dorsalis, are reported. Although this association was recognized many years ago, it has received little attention in recent medical literature. Its recognition is important, not only in the management of tabes dorsalis but also in avoiding needless surgical exploration of the adrenal glands.

ADDENDUM

Since this paper was submitted for publication, our attention has been called to several other patients who have had paroxysmal hypertension associated with tabes. Rowntree and Ball (*Endocrinology*, 17: 263-299, 1933) reported a patient with tabes in whom the suspected adrenal tumor was found neither at operation nor at autopsy. Adrenal exploration was also performed in a woman with fixed pupils and a history of syphilis in whom marked elevation of blood pressure occurred during tabetic crises (personal communication, Dr. Augustus S. Rose, Boston). This patient also had a bilateral splanchnicectomy without any change in blood pressure when last seen. A third patient with severe tabes was recently seen at Duke University Hospital and demonstrated both paroxysmal hypertension and postural hypotension (personal communication, Dr. John Hickman, Durham).

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Cardiac Pain*

Present Status of Its Mechanism and Therapy

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THE association of pain in the chest with heart disease is mentioned in the memoirs of the Earl of Clarendon in 1632.¹ Willius and Dry² record two other early references to this correlation.^{3,4} William Heberden⁵ was the first to describe "dolor pectoris" as a "disorder of the breast marked with strong and peculiar symptoms . . . the seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly called angina pectoris." However, Heberden never truly discerned that the heart was the organ responsible for the seat of origin of this pain and it remained for Jenner⁶ in 1799 to demonstrate a causal relation between the two. Although Black⁷ published this clinical observation before Jenner, it is known that Jenner had related pain in the chest to heart disease in his friend, Hunter, in 1772.

It was not until about 150 years later that James B. Herrick's description of coronary thrombosis in 1912⁸ made this disease a recognized clinical entity. "I have seen five other cases that I am convinced were instances of coronary thrombosis, the patients living many hours after the accident, though no autopsy control confirms this opinion. All were men beyond 50. In all there was some evidence of peripheral arteriosclerosis; all had had previous anginal attacks. In all, the final attack was described as the severest and most prolonged in the experience of the patient. Morphine alone had given relief."

MECHANISMS

The aims and results of therapy for cardiac pain are directly linked to the mechanism for initiation and maintenance of such pain. It follows then that this review must begin with the present status of our knowledge in regard to nerve pathways for the conduction of pain impulses from the heart.

Afferent Pathways for Cardiac Pain. The afferent pathways for pain from the heart begin in the sensory nerve endings which are present in the adventitia of the coronary arteries and questionably in the myocardium, endocardium and epicardium.^{9,10} The nerve fibers from these receptors collect in the superficial and deep cardiac plexuses. They travel centrally by way of the middle and inferior cardiac nerves to the cervical sympathetic ganglia, and by way of the thoracic cardiac nerves to the upper four or five thoracic sympathetic ganglia.¹¹⁻¹⁷ Since there are no white rami which connect the cervical sympathetic chain and the spinal cord, it had been generally assumed that these cardiosensory fibers must pass down the sympathetic chain to the upper thoracic sympathetic ganglia and from there proceed through the white rami communicantes of the first thoracic and upper four or five intercostal nerves to reach their cell bodies in the posterior root ganglia. Thus, the first neuron in this afferent system has its cell origin in the dorsal root ganglion and its synapse in the dorsal horn.

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Wolff and Hardy¹⁸ trace noxious impulses giving rise to pain after entering the cord as follows: "they are conveyed across to the opposite side where their pathways are localized in the antero-lateral portion of the spinal cord. The fibres of the spinothalamic tract pass into the nucleus centralis posterior of the thalamus. They do not terminate in any of the adjacent nuclei nor go into the anterior portion of the thalamus. The cortical projection from the nucleus centralis posterior is predominantly to the post-central convolution. There is in this projection a definite topical organization so that those fibres from the medial portion of the nucleus (cephalad parts of the body) end in the lower part of the gyrus; those from the lateral portion (caudad parts of the body) in the paracentral region; and those from the middle, in the intermediate region."

Surgical interruption of the cardiosensory tracts at various levels is based on an understanding of these pathways.

Somatic Reference of Cardiac Pain. Pain which originates in the heart is known to be commonly referred to the jaw, neck, chest, to either shoulder or arm down to the fingertips, to the back and to the epigastrium.

The theories concerning the mechanism of the production of referred pain apply to that from the heart just as from other viscera, namely, referred pain is due either to poor localization by the cerebral cortex or to an "irritable focus" in the spinal cord.¹⁹ Lewis²⁰ is the chief proponent of the first of these two theories. He states that segmental reference of visceral pain is due simply and entirely to the poor localizing powers of the brain. "And it may be regarded as natural enough that the general reference should be to regions that are relatively superficial, regions from which we are habitually receiving sensory impressions and which are endowed with some positional sense."

The irritable focus theory, which is that of the school of Ross, Head and McKenzie,²¹⁻²³ holds that painful visceral impulses on reaching the spinal cord set

up a disturbance or irritable focus which extends to nerve fibers from the body surface. Since sensation from the body surface is the more highly developed, pain is then referred to the periphery from which painful stimuli are usually initiated.

Mention has been made recently of some of the pathways for segmental reference of pain from the heart to the periphery. Involvement of the lower jaw and teeth in referred pain of cardiac origin is explained¹⁸ by the spread of pain impulses from the thoracic segments headward so as to "seem to arise within the structures supplied by the lower cervical segments." This involves the cervical dorsal horn and the descending nucleus of the trigeminal nerve.

Judovich²⁴ believes that the common afferent pathway for referred pain from the heart is the phrenic nerve which originates from segments C₃, C₄ and C₅. Thus, somatic structures similarly innervated by these segments will be involved in the zone of reference. This would include many of the muscles of the shoulder girdle and upper extremity. Stimulation of the phrenic nerve would result from pericarditis which accompanies acute myocardial infarction.

Roberts²⁵ postulates a common segmental origin for the vasomotor nerves in the walls of the blood vessels which supply the cardiac nerves and for the branches of the brachial plexus. Ischemia or disease involving the blood supply to the cardiac nerves may by reflex cause vasospasm in the nerves of the precordium and upper limb and serve as the mechanism for referred cardiac pain.

While it is understandable that a continued reference of pain would occur in the presence of an active visceral lesion, persistence of pain in the chest when painful visceral impulses no longer are present needs elucidation. Rinzler and Travell²⁶ explain this persistence of pain in somatic structures by the following: the initial insult to the heart leads to the development of somatic trigger areas within the "reference zone" of the visceral lesion. Even though the noxious impulses from the primary source in the heart may cease, pain

in the chest continues because of an autogenic cycle of nerve impulses maintained by the secondary sources in the somatic structures. This theory serves to elucidate the mechanism for persistent chest pain postinfarction and for establishment of the "frozen shoulder" syndrome seen in coronary artery disease. Elimination of the trigger areas and pain by local infiltration of procaine hydrochloride or local spray with ethyl chloride adds weight to this concept of referred pain. This will be discussed in detail later.

Experimentally Induced Cardiac Pain. The stimulus for cardiac pain has been variously attributed to: (1) distention of the coronary arteries or aorta, (2) anoxia of the myocardium (dependent on a reduced blood flow through the coronary arteries), (3) accumulation of metabolites of muscular contraction.

Distention: In 1924, Wenckebach²⁷ postulated that sudden distention of the aorta or distention of the coronary arteries proximal to the point of occlusion stimulated the nerve plexus in the adventitia of the vessels. This idea was extended by Martin and Gorham²⁸ who obtained typical pain responses in dogs (increase in heart rate, dyspnea and movement of the left foreleg) when tridirectional tension in one plane was applied to the coronary vessels in such a manner as to cause no change in blood flow. The proposition that arterial distention in a viscus may be the seat of pain has been given weight by the work of Wolff²⁹ who demonstrated that intracranial arterial distention gave constant patterns of referred pain in the head.

Anoxia: Keefer and Resnik³⁰ in a classical paper on angina pectoris suggested that this symptom "was due to anoxemia of the myocardium, that is, the attacks occur when the oxygen supply to the heart is inadequate to meet the oxygen demands of the heart." Sutton and Lueth³¹ provided experimental data to support the anoxia theory in a study on dogs in which a ligature was placed around the left anterior descending branch of the coronary artery and the chest

wall was closed. Pulling on the vessels temporarily reduced the blood flow and resulted in pain. They disagreed with the distention theory by showing that the closure of the coronary artery orifice in the aorta produced pain without distention. Also, acute mechanical distention of the aortic arch, aortic ring and cavity of the left ventricle did not produce pain. White, Garrey and Atkins³² used a similar type of animal preparation and were able to confirm the experiment of Sutton and Lueth. Blumgart³³ concluded, on the basis of his extensive pathologic experience with human hearts, that the ischemic theory for cardiac pain is a correct concept.

Metabolite Accumulation: In 1932, Lewis³⁴ postulated that in attacks of angina pectoris a condition of relative work-ischemia occurs because of limited blood flow with the accumulation of a "P" substance which initiates the painful stimuli. In normal conditions the "P" substance produced by muscular effort is removed by an adequate blood flow.

Katz^{10,35} states that "it is not clear whether it is an acid metabolite like lactic acid, phosphoric acid, pyruvic acid or succinic acid, or is a non-acid metabolite like histamine, phosphocreatine, adenosine, or potassium." These non-volatile, diffusible metabolites are probably manufactured by the heart muscles under all ischemic conditions but may not always be present in sufficient amounts to stimulate end organs for pain.

In summarizing these theories then one may conclude that there is no definite proof as to whether anoxia (oxygen deficiency) or ischemia (reduction of blood flow) predominates either singly or in combination in inducing pain of cardiac origin. Lewis found that occlusion of the arterial supply to the forearm by means of a blood pressure cuff for as long as twenty minutes produced no pain until active skeletal muscular contraction was begun. However, it is possible that such a deficiency of oxygen may have hastened the process that led to pain since pain will appear in working skeletal muscle

that is well supplied with blood but is made deficient in oxygen by breathing a low oxygen mixture. Since cardiac musculature is constantly in a state of active contraction during life, no data can be gathered for the heart similar to those for resting ischemic skeletal musculature. A relative state of work-ischemia can be set up experimentally in the human by means of the exercise tolerance test of Master.^{36*} A relative state of anoxia of cardiac musculature is induced by the anoxemia test.^{37†}

Since anoxia causes a profound increase in coronary blood flow³⁸ and since a state of work-ischemia exists in the overtaxed heart with coronary disease, it seems reasonable to assume that stimulation of end organs for pain by metabolite accumulation in working cardiac muscle in the anoxic state is responsible for pain rather than the anoxic or ischemic state *per se*. It is this reasoning that enables one to understand why the functional efficiency of coronary circulation can be tested by either the exercise tolerance test or the anoxemia test. In each instance we are dealing with a constantly working muscle of the heart in which the process of metabolite accumulation is hastened by exercise or anoxia.

* Master introduced this "two step" test of cardiac function in 1929. The number of trips over the steps is standardized according to age, weight and sex and is performed in ninety seconds with recordings of blood pressure, pulse and electrocardiograms before and after the test. In normal persons the blood pressure and pulse should return to within ten points of resting levels in two minutes. Electrocardiographic changes which are considered significant of heart disease are as follows: (1) a depression of the RS-T segment of more than 0.5 mm. in any lead; (2) a change from an upright T wave to an isoelectric or inverted T wave or (3) a change in the T wave in the opposite direction.

† A 10 per cent oxygen and 90 per cent nitrogen mixture is used. This mixture is breathed for twenty minutes or until pain is felt in the chest. Electrocardiograms are taken before the start of the test and at ten and twenty-minute intervals after it. The result is positive for coronary insufficiency when any one of the following is found in the electrocardiogram: (1) The arithmetic sum of the RS-T deviations in all four leads (I, II, III and IVF) is greater by 3 mm. or more than is the control. (2) There is partial or complete reversal of the direction of the T wave in lead I accompanied by an RS-T deviation of 1 mm. or more in this lead. (3) There is complete reversal of the direction of the T wave in lead IVF regardless of any associated RS-T deviation in this lead.

THERAPY

Efforts to relieve pain of cardiac origin have centered about the following methods: (1) increasing the blood supply to the heart either through existing channels by dilating the coronary arteries or by creating new arterial channels surgically; (2) insuring that the patient's activities and metabolism are brought down to the level of the circulation available and (3) by interrupting the pain pathways at some point between the heart and the brain.

Evaluation of Therapy. The difficulties of assessing the value of drug therapy in relieving cardiac pain are a product of the limitations in quantitative methods of analysis and the numerous factors other than drug therapy that influence the pain. Thus, Gold³⁹ lists the following circumstances which influence the daily course of anginal pain: (1) spontaneous variations in the course of the pain, (2) changes in the weather, (3) a change of occupation or amount of work, (4) changes of diet, (5) changes in eating habits with increase in the amount of rest before and after meals, (6) condition of the bowels, (7) emotional stress, (8) a change in domestic affairs, (9) confidence aroused in treatment, (10) encouragement afforded by any new procedure and (11) a change of medical adviser.

Methods. Gold³⁹ has chosen the "blind" test for evaluation of therapeutic response. In this method the drug used is unknown to both the doctor and patient and all medication given is, as far as possible, similar in size, shape and taste. The patient is followed over a sufficiently long period so that the extraneous factors previously mentioned are eliminated. By this method it is believed that the relief of pain during use of any drug is due to its specific action. The patient should be able to distinguish its effects and to do so repeatedly from the effects of a placebo given under similar conditions and in such form as to preclude its detection by the patient through any means other than the relief of pain.

Riseman⁴⁰ has devised a standard exercise tolerance test which consists of walking up two steps and down two steps (each step is 9 inches high) until an attack of pain ensues. This test is made under the standard conditions of (1) a low temperature of 45 to 55°F., (2) one hour after a light meal, (3) no recent attack, (4) no medication and (5) familiarity with the test. A precordial lead of the electrocardiogram is also taken before and after exercise to determine the depression of the RS-T segment. A therapeutic effect of any drug depends on the increase in exercise tolerance and no change in the electrocardiogram.

We have modified this technic⁴¹ to the extent that a control test with a placebo is done each time that a drug is studied. This is carried out because of the day to day variation in the exercise tolerance of the patient. This gives each test its own daily control. During these tests both the placebo and medication are unknown to the patient and the physician. No electrocardiograms are taken.

It has been our experience that evaluation of drug therapy for cardiac pain which does not make use of some method of blind testing is open to serious question. This cannot be overemphasized.

CORONARY VASODILATORS

1. *Nitrites.* Brunton⁴² reported on the use of amyl nitrite in angina pectoris in 1867, "on pouring from five to ten drops of the nitrite on a cloth and giving it to the patient to inhale, the physiological action took place in from thirty to sixty seconds; and simultaneously with the flushing of the face the pain completely disappeared and generally did not return till its wonted time next day." In 1879, Murrell⁴³ indicated that equally successful results could be obtained with nitroglycerine (glyceryl trinitrate). Bradbury⁴⁴ introduced erythrol tetranitrate in 1895.

Pharmacologic Basis of Action: Use of nitrites in the relief of pain of angina pectoris depends on their relaxation of the coronary vascular tree.⁴⁵ Coronary vaso-

dilatation outlasts the effects of nitrites on other vascular beds and coronary blood flow is increased despite the concomitant fall in aortic pressure. The nitrites increase coronary arterial blood flow.^{46,47}

Preparations and Dosage: (1) Amyl nitrite in pearls containing 0.2 cc.; (2) tablets of glyceryl trinitrate (nitroglycerine), 0.6 mg.; (3) octyl nitrite, 2. cc. put up in inhaler form;⁴⁸ (4) sodium nitrite, 15 to 60 mg. every three to four hours; (5) erythrol tetranitrate, 30 to 60 mg. every three to four hours. Action begins in fifteen minutes and lasts from three to four hours; (6) mannitol hexanitrate, 15 to 60 mg. every four to six hours. Action begins in fifteen to thirty minutes and lasts from four to six hours.

Side Reactions: The nitrites may cause flushing, headache, throbbing, palpitation and cardiovascular collapse. Mannitol hexanitrate may also cause methemoglobinemia, a rise in intraocular pressure or an increase in intracranial pressure.

Comment: The nitrites are the drugs of choice in combatting acute pain of effort angina. The quick-acting nitrites (amyl nitrite and glyceryl trinitrate) are used as diagnostic drugs to differentiate the pain of angina pectoris from other causes of chest pain. This, however, also has its pitfalls for Gold³⁹ has shown that many patients obtain equal relief with placebos placed under the tongue as with glyceryl trinitrate. Studies have also been made^{40,49} on the prophylactic use of longer-acting nitrites in angina pectoris. The general consensus with use of erythrol tetranitrate or mannitol hexanitrate is that no great advantage is to be found over treating the individual attack. Gold⁵⁰ has pointed out that the frequent use of nitrites will neither lead to dependence on them or reduce their efficacy.

2. *Xanthines.* In 1895, while working with diuretics, Askanazy⁵¹ noted that theobromine sodio-salicylate, besides its diuretic action, was also useful for pain in angina pectoris.

Pharmacologic Basis: There is ample experimental evidence to prove that xanthines

are coronary vasodilators.⁵²⁻⁵⁴ Fowler, Hurevitz and Smith⁵⁵ studied the effects of aminophylline on experimentally-induced cardiac infarcts in dogs. They found the infarcted area considerably less in the aminophylline-treated dogs than in the controls and concluded that the theophylline-ethylenediamine was capable of developing collateral coronary circulation in the dog. Gold, Travell and Modell⁵⁶ repeated this work in cats and measured the size of the infarcts with a planimeter. They could not confirm the results of Fowler.

Preparations and Dosage: Clinical studies in angina pectoris have been made with theobromine (0.3 to 0.6 Gm. 4 times a day); theobromine sodio-acetate (0.45 to 0.7 Gm. 4 times a day); theobromine sodio-salicylate (0.5 to 0.7 Gm. 4 times a day); theobromine calcium salicylate (0.5 to 1.0 Gm. 4 times a day); theophylline (0.1 to 0.25 Gm. 4 times a day); theophylline sodio-acetate (0.2 to 0.3 Gm. 4 times a day) and theophylline-ethylenediamine (aminophylline) (0.1 to 0.2 Gm. 4 to 6 times a day).

Side Actions: The main disadvantage of oral administration of xanthines is occasional gastric irritation. Intravenous administration may produce giddiness, excitement, faintness, flushing, tingling of lips, collapse and death.

Comment: The original enthusiasm for use of xanthines orally in angina pectoris^{57,59,63,64} was followed by discouraging reports.⁶⁰⁻⁶² Finally in 1943 in a review for the Council of Pharmacy of The American Medical Association, Boyer⁶⁵ concluded that "the clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory. It seems wise to place the burden of proof on those who claim therapeutic efficacy."

Because of the discouraging results with oral administration of aminophylline, we investigated its usefulness in angina of effort by intravenous administration.⁴¹ It was found that an intravenous injection of 0.24 Gm. of aminophylline increases the capacity for effort without pain in patients

with angina of effort and that this effort without pain lasts longer than one hour. It is obvious, however, that this method of administration is of limited practical value.

3. *Papaverine.* Pal⁶⁶ in 1913 first advocated the use of papaverine in treatment of angina pectoris.

Pharmacologic Basis: Macht^{67,68} found papaverine to be a powerful dilator of the coronary arteries of frogs. The studies of Essex⁶⁹ in dogs further corroborated the coronary vasodilator action of papaverine.

Preparation and Dosage: Papaverine hydrochloride is given orally in doses of either 33, 100 or 200 mg. four times daily. The intravenous dose is 65 or 100 mg.

Side Actions: Papaverine may cause dizziness, nausea, vomiting, drowsiness, auriculoventricular and intraventricular block, cardiac arrest, premature beats, coupling, ventricular tachycardia and fibrillation.

Comment: There is diverse opinion as to the efficacy of oral doses of papaverine for relief of angina pectoris. Pal,⁷⁰ Boehm,⁷¹ Macht,⁶⁸ and Katz and Elek⁷² report favorable effects in angina pectoris. Pal and Macht gave their doses intravenously (30 and 40 mg.). Boehm and Katz and Elek gave their medication orally, the latter investigators in doses of 100 mg. four times daily. Gray, Riseman and Stearns⁷³ also found the drug of value for pain in coronary insufficiency and coronary thrombosis when given intravenously in doses of 65 or 100 mg. They found, however, that oral doses of 33, 100 or 200 mg. four times daily for one week were of little value in clinical treatment of angina pectoris.

This same mixed feeling was expressed by Gold⁷⁴ in a recent review of the value of papaverine in coronary artery disease. He believed that it had some value but how much was still in doubt. Its administration was not without dangers. These include toxic rhythms, namely, premature beats, coupled rhythm, ventricular tachycardia and partial A-V block, all which may occur with doses within the therapeutic range.

4. *Ethyl Alcohol.* This is a commonly used remedy for anginal attacks. Its use is

based on the concept that it is a vasodilator. However, Dixon⁷⁵ found experimentally only slight vasodilation of the coronary arteries. Evans and Hoyle⁷⁶ found that objectively only one in eleven patients was able to do more work following prophylactic use of brandy. Stearns et al.⁷⁷ found that therapeutic doses of whisky (1 ounce) did not measurably shorten the duration of attacks of angina pectoris or increase the capacity of the patient for work. Eggleston,⁷⁸ however, recommends a small drink of brandy or whiskey to relieve the pain of angina pectoris.

The effects of alcohol in relief of angina must be attributed to its central action in dulling response to pain rather than its coronary vasodilator action.

MISCELLANEOUS AGENTS

1. *Androgens.* The basis for use of androgens in the treatment of angina pectoris was the finding of Edwards, Hamilton and Duntley by spectrophotometric studies that the diminished arterial supply to the skin of castrated men was increased after administration of testosterone propionate.⁷⁹

Dosages: A dose of 25 mg. of testosterone propionate twice weekly seems to be the average dose. Frequency of medication and duration varies with different investigators.

Side Actions: Testosterone therapy can cause marked sodium chloride and water retention and on occasion may precipitate cardiac failure.⁸⁶

Comment: The majority of investigators^{80-82,84-86} report some degree of improvement in the pain of angina pectoris under therapy with testosterone propionate. Riseman,⁸⁸ Levine and Likoff⁸³ and Levine and Sellers⁸⁷ give an unfavorable report. Lesser⁸⁶ attributes this lack of success to insufficient treatment since about one-third of his group showed no noticeable improvement during the first month of therapy. In Lesser's study also the possible psychologic effect of injection therapy *per se* was eliminated by giving five patients six consecutive injections of sterile sesame oil

prior to receiving testosterone propionate. None of the patients on sesame oil showed any appreciable change in symptoms while progressive improvement occurred in the same patients following use of hormone therapy. Sigler and Tulgan⁸² also used this technique. However, the study was not an entirely blind one. In both instances the physician knew when he had given a placebo. This may have prejudiced his questioning of the patient. Other than this criticism one must remember that testosterone propionate therapy is costly and must be given parenterally.

There is no adequate explanation for the apparent efficacy of androgen therapy in angina pectoris. Waldman⁸⁵ has postulated that testosterone may act in a number of ways: by vasodilatation of the coronary arteries; by development of a collateral circulation; by correction of an androgen deficiency or by an improved cardiac muscle metabolism of phosphorus and creatine.

2. *Cobra Venom.* Freedberg and Riseman⁸⁸ found that administration of cobra venom to patients with angina pectoris increased the standardized exercise tolerance in seven of twelve patients studied. Since in these patients medication did not prevent the electrocardiographic changes associated with exertion, they concluded that the action was not one of coronary vasodilation. The dose was 10 mouse units three times the first day, followed by one injection daily for seven days and then biweekly injections of the same dose.

3. *Radiation Therapy.* Sussman⁸⁹ found that suberythema or slight erythema doses of x-ray given over the lower cervical and upper dorsal spines to include the sympathetic ganglia caused improvement in the anginal attacks in eleven of sixteen patients. We have found a number of patients with heart disease and cervical or thoracic spondylitis whose chest pain was greatly relieved by cervical and dorsal radiation. We have no experience in the effect of radiation therapy on patients with no vertebral osteo-arthritis.

Raab⁹⁰ was able to improve the anginal attacks in 74 per cent of forty-two patients by radiation of the adrenals, the rationale being the decrease in the anoxiating effect of adrenalin on the heart muscle by an abolition of the abnormal irritability of the adrenal secretory mechanism.

McMillan and his co-workers^{91,92} irradiated the adrenal glands of twenty-three patients with severe angina pectoris. Each adrenal area received 600 r in three divided doses a week. Thirteen patients were greatly relieved, four moderately, three slightly and three not at all. These patients were observed for a period of from two to twelve months. The treatment did not alter the life expectancy.

4. *Vitamin E.* Shute, Shute and Vogel-sang⁹³ report on eighty-four patients suffering from anginal pain who were treated with a dosage of vitamin E ranging from 150 to 600 mg. (in terms of alpha tocopherol). Relief commenced in approximately five to fourteen days. The maintenance dose was about 150 to 200 mg. per day. They suggested that no iron be administered with vitamin E. Fifty mg. of the natural mixed tocopherols are about equal to 25 mg. of the alpha tocopherol.

On this regimen⁹⁴ six (7 per cent) of the eighty-four patients had complete relief of anginal pain, thirty-eight (45 per cent) had great improvement, thirty-seven (44 per cent) had some improvement, two (3 per cent) had no improvement and one (1 per cent) died.

Ravin and Katz (personal communication), of the Boston City Hospital, tried 500 mg. of mixed tocopherols (alpha tocopherol, 50 per cent) daily in two divided doses in eleven patients with undoubted angina pectoris. Ten patients had arteriosclerotic or hypertensive and arteriosclerotic heart disease; one patient had luetic heart disease. The treatment varied from four weeks (two cases) to twenty-four weeks (three cases), averaging fourteen weeks for the group.

The results, as measured by (1) exercise tolerance tests, (2) consumption of nitro-

glycerine per day before and during vitamin E therapy and (3) subjective improvement, revealed no objective or subjective improvement in any patient in the entire group.

5. *Cytochrome C.* Cytochrome C acts by enhancing the tissue uptake of oxygen. For this reason Procter⁹⁵ has used this in patients with myocardial anoxia. Cytochrome C, 60 mg. intravenously, has been shown to prevent anoxic changes in the electrocardiogram of cardiac patients brought on by breathing a 10 per cent oxygen mixture.

We have given 50 mg. of cytochrome C intravenously to test the effect on the capacity for effort of patients with unequivocal angina pectoris and found the drug to be of no value.⁹⁶

SURGERY

Surgery for the relief of cardiac pain centers about three methods of attack: (1) creating new channels of blood supply, (2) thyroidectomy, (3) interruption of the sensory pathways.

1. *New Channels.* The methods for surgically altering the blood supply to the myocardium have been summarized by Beck.⁹⁷ The most popular is by establishing vascular communications between the coronary arteries and the arteries of tissues engrafted upon the heart. The tissues that have been used for this purpose include the parietal pericardium, mediastinal fat, skeletal muscle from the chest wall and omentum brought up through an opening in the diaphragm.⁹⁸⁻¹⁰² The tissues are engrafted by sutures except for the cardiopericardiopexy when chemical agents are used¹⁰³ for the purpose of producing an inflammatory reaction between the heart and parietal pericardium.

Experimental ligation of the coronary veins and experimental removal of nerves at the base of the aorta and in the region of the left coronary artery have been shown to improve coronary artery circulation. Fauteux^{104,105} has reported on the use of pericoronary neurectomy plus ligation of the great cardiac vein in the treatment of angina pectoris in man.

2. *Thyroidectomy.* Total ablation of the thyroid by surgical means¹⁰⁶ is used to relieve precordial discomfort of angina pectoris. It has greater use in the treatment of congestive heart failure. The efficacy of the method is based on the idea that following total thyroidectomy, the metabolic needs of patients with heart disease are decreased considerably and therefore the work of the heart is lessened with a concomitant relative increase in circulatory adequacy. The operation is complicated by the need to remove every vestige of thyroid tissue without injuring the recurrent laryngeal nerves or removing the parathyroids.

Because of these possible complications, introduction of the thiourea derivatives was suggested as a medical means of inducing chemical thyroidectomy. Encouraging results have been reported with its use in angina pectoris.¹⁰⁷⁻¹⁰⁹ According to Raab,¹⁰⁷ the thyroid hormone even in physiologic amounts sensitizes the heart to the anoxiating toxic action of epinephrine. Thiouracil exerts a "heart protecting" effect by suppressing the formation of thyroid hormones. He found thiouracil treatment effective in seven of ten patients with angina pectoris. Ben-Asher¹⁰⁸ found clinical improvement in twenty-five of thirty-seven (67 per cent) patients with angina pectoris given 0.4 to 0.6 Gm. of thiouracil daily for at least three weeks followed by a daily maintenance dose of 0.2 Gm. Reveno reported favorable results with both thiouracil and propylthiouracil (75 to 125 mg.) daily.

DiPalma and MaGovern¹¹⁰ caution that as the basal metabolic rate is lowered by thiouracil there is a tendency for water retention to occur so that pulmonary edema and increased dyspnea appear. They further show that those patients who benefit mostly from thiouracil administration have an elevated basal metabolic rate before treatment. They conclude that this is the only indication for use of the drug other than as a therapeutic test in selection for thyroid-

ectomy in those patients with angina pectoris.

3. *Interruption of Sensory Pathways.* From knowledge of the anatomic pathways for the sensation of pain of cardiac origin one readily realizes that pain can be eliminated by blocking the pathway at any point between the heart and brain. Fauteux¹⁰⁵ starts close to the heart and does a pericoronary neurectomy similar to the periarterial stripping in animals.

The upper thoracic sympathetic ganglia are by far the areas of choice for interrupting pain sensations.¹¹¹⁻¹¹³ This may be done in three ways: First, the sympathetic ganglia may be infiltrated with procaine hydrochloride or alcohol to produce a block of a more or less temporary nature. Second, the sympathetic chain may be resected either unilaterally or bilaterally so as to interrupt the visceral afferent fibers going to the cord. Third, the first four or five posterior roots may be cut through a laminectomy. Such posterior rhizotomy (division of the non-myelinated axon of the peripheral sensory ganglion) should be carried out bilaterally for permanent effect.

The latest report on the number of sympathetic ganglia that must be blocked for relief of pain is by Saccomano, Utterback and Klemme.¹¹⁴ They believe that surgical removal or alcohol injection of the second, third and fourth thoracic sympathetic ganglia on the affected side only will alleviate anginal pain. This is based on experiments upon dogs in which stimulation of C₈ and T₁ when isolated produced no effect on the heart rate or blood pressure. The effect on pulse rate was most marked on stimulating the second and third thoracic nerves with diminishing effect on the fourth and fifth thoracic nerves. The effect on systemic blood pressure was more or less constant from the second thoracic nerve down to the seventh thoracic nerve.

While investigating a group of patients with pain in the chest and pain and limitation of motion in the shoulder,¹¹⁵ Travell and Rinzler^{26,116} confirmed the early work

of Weiss and Davis¹¹⁷ and found that this pain and disability could be relieved by local block, either by infiltration with procaine hydrochloride or spray with ethyl chloride, of tender areas located in the muscles of the chest wall anteriorly or posteriorly. These tender or trigger areas were defined as points of abnormal hypersensitivity of the myofascial structures which on stimulation (either by mechanical pressure or needling) gave rise not only to local pain but to referred pain at a distance from the trigger area. The area of referred pain was in the same region as that of the spontaneous pain, for example, spontaneous pains in the regions of the shoulder and arm were referred pains from either the infraspinatus, supraspinatus or pectoralis minor muscles.

Although the majority of these patients were non-cardiacs, it soon became evident that the same procedure was effective in relief of chest pain in patients with myocardial infarction and angina pectoris. The trigger areas in these cardiacs were located mainly in the intercostal spaces at about the nipple line in the pectoralis major and minor muscles. In these muscles the referred pain tended to circumscribe the trigger areas.

It was obvious to us from the onset that extreme care had to be taken in attributing success to any treatment for chronic angina pectoris because of the multiplicity of non-specific procedures which are therapeutic. However, we were fortunate in obtaining a number of patients in whom acute myocardial infarction without previous history of angina of effort had produced chest pain and trigger areas in the chest and in whom local block therapy was completely effective when opiates were not. These acute observations in our opinion gave weight to the rôle of the somatic component in cardiac pain.

In a study²⁶ of thirty-one patients with chest pain due to coronary artery disease who presented tender areas in the anterior chest muscles, we found the following: satisfactory results with local block therapy

were obtained in those patients in whom angina of effort began after a myocardial infarction or in whom a history of a myocardial infarction in the course of effort angina could be obtained. Unsatisfactory results were obtained in those patients whose angina of effort was insidious in onset and in whom no history of a myocardial infarction could be elicited. Comparison of the two groups as to age, sex, incidence of hypertension or duration of symptoms revealed no differences. We sought to explain the differences in results in the part played by the heart and soma in the summation of pain. That is, in the cases of angina pectoris without myocardial infarction we assumed that the stimulus for pain proceeded directly to the sensorium with little involvement of the soma or that the soma played a small rôle in the total summation of pain. Furthermore, repetitive attacks of angina tend to set up new areas of referred pain in the chest muscles. On the other hand, in the postinfarction group we reasoned that stimuli for pain from the heart no longer existed after the acute myocardial infarction or else that the somatic components in postinfarction angina of effort played a predominant rôle and, therefore, its elimination by local block resulted in a state in which stimuli from the heart alone were subthreshold and, therefore, not of sufficient intensity to produce pain.

We postulated that the tender areas in the chest muscles were set up by development of trigger areas in the reference zone of the visceral lesion. These secondary sources in the somatic structure then set up their own autogenic cycle without further dependence upon the heart.

SUMMARY

1. The nervous system pathways involved in transmission of impulses of pain from the heart and to its regions of reference are described.

2. Stimulus for cardiac pain seems to depend on accumulation of metabolites in working cardiac muscle in the anoxic state.

3. The relative efficacy of such drugs as the nitrites, xanthines, papaverine, alcohol, androgens, thiourea compounds and others is discussed.

4. The surgical procedures for relief of cardiac pain, directed either at increasing the blood supply to the heart, or reducing the metabolic activity of the patient or interrupting the afferent pain pathways, are described.

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Seminars on Protein Hydrolysates

Problems of Parenteral Nutrition*

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ALMOST all of the essential materials for adequate parenteral nutrition are in present day use. The possibilities of giving glucose by vein were explored by Woodyatt et al. in 1915.¹ The importance of salt replenishment has been recognized since 1831²⁻⁴ although later work has stressed the value of other electrolytes as well.⁵ Many of the vitamins have been made available for parenteral administration and their use today is commonplace. Fat emulsions with their potentially high caloric content have been given intravenously to patients⁶⁻⁸ but this use is still investigative. Finally, parenteral solutions containing nitrogen have advanced from the laboratory stage to daily practice. These last provide potential protein and have made complete nutrition independent of the gastrointestinal tract a reality.⁹⁻¹²

The first readily available⁹ preparation of an enzymatic hydrolysate of casein is now in widespread clinical use, and other more concentrated and more purified products have been introduced by vigorous commercial effort in this field. Complete parenteral feeding for twenty-four days without mishap has been accomplished with these preparations.¹³ However, the thesis that starvation is inherently harmful even for short periods and should be avoided has led at times to the indiscriminate use of these materials. It is still debatable whether the results of routine parenteral feeding warrant the risks and discomfort to the patient as well as the expense. Thus a careful appraisal of the effect of these nitrogen-containing materials

given in the postoperative period to patients undergoing subtotal gastrectomy for peptic ulcer cannot be said to show more than a suggestive gain over an adequate control series treated exactly the same, except for the parenteral nitrogen.¹²

In addition, there are many problems which arise during vigorous therapy with the precursors of protein given parenterally. Such treatment is subject to accidental or unavoidable interruption. Changes then follow, in terms of nitrogen balance, which are of considerable interest since fairly large losses of nitrogen may result. This point has not received much attention; also, the extent of the caloric intake which must be provided with the protein, in order to conserve nitrogen, has not been entirely settled. It is the primary purpose of this review to discuss these problems and to summarize some of the difficulties in the practical execution of parenteral feeding programs. It is intended to extend, rather than to repeat, the discussions in the extensive reviews by Elman¹⁴ and by Kremen.¹⁵

Parenteral feeding can be used to supplement limited food intake by mouth or to replace food entirely when the oral route is not available. The body is capable of undergoing complete¹⁶ or partial starvation¹⁷ for brief periods of time without too great apparent harm although capacity for work is probably reduced.¹⁸ The effects of prolonged malnutrition, including the complications of hypoproteinemia,^{14,19,20} have been stressed elsewhere and need no elaboration here. Thus, during brief periods of inadequate dietary intake in the previously

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well individual, it is a matter of clinical judgment as to whether parenteral supplementation really is necessary or need be undertaken. In the previously depleted individual, however, or when the period of inadequate food intake has been prolonged, there is little doubt that supplementary feeding is desirable. However, a decision to employ parenteral feeding may be contraindicated by other considerations; these will be discussed later in the article.

The major situations in which some form of parenteral replacement, whether nitrogenous or otherwise, may become of importance are outlined. Indications for therapy are found in the shock, dehydration, acid-base balance disturbance, hypoproteinemia and anemia which may accompany most of these disorders.

INDICATIONS FOR PARENTERAL THERAPY

1. *Disorders of Ingestion*.—Functional: Anorexia associated with physical difficulties such as pain, disease and trauma. Anorexia associated with emotional difficulties for example, psychoneurosis such as anorexia nervosa; pylorospasm or cardiospasm, functional: fear of discomfort after eating. Mechanical: Disorders of the esophagus such as inflammation, carcinoma, ulceration, stricture or diverticulum. Disorders of the stomach and duodenum such as pyloric stenosis or spasm secondary to ulcer; pyloric stenosis or spasm secondary to carcinoma; duodenal stasis; duodenal obstruction from whatever cause; in early postoperative states such as atony, edema or distention and late postoperative states as gastro-enterostomy, stenosis or ulceration. Small and large intestinal disorders such as mechanical ileus from adhesions, carcinoma, lymphoma, herniation, etc.; paralytic ileus from toxemia or peritonitis; postoperative state of atony, distention or edema.

11. *Disorders of Absorption*.—Failure of small intestinal function: *Normal transit time* affected by inadequate intestinal length—internal or external fistula; resection of small and large intestine with high ileostomy; gastrocolic or jejunocolic anastomosis; and inadequate enzyme secretion because of sprue and non-tropical sprue or pancreatic disease. *Decreased transit time* due to infection, e.g., tuberculosis, typhoid

fever; inflammation, regional ileitis; reflex, secondary to colitis, e.g., ulcerative colitis, amebic dysentery, etc. Failure of bile secretion with failure of fat digestion because of obstruction or fistula.

111. *Disorders of Utilization*.—Decreased utilization: Failure of protein synthesis because of hepatitis; cirrhosis, Laennec's or obstructive; idiopathic hypoproteinemia. Failure of carbohydrate metabolism because of diabetic acidosis. Increased utilization: Toxic goiter; fever; post-trauma; insulin shock; suppuration, wound or skin ooze.

1V. *Hemorrhage, Dehydration and Shock from Any Cause*.

The aforementioned situations may necessitate parenteral therapy with some or all of the materials now available for use by this route. For this reason, and because any program using nitrogenous materials must take into account the provision of calories and electrolytes as well, a brief summary of these latter materials and the problems associated with their administration is introduced here.

NUTRITIONAL FACTORS IN PARENTERAL THERAPY

Electrolytes. Use of electrolyte solutions in the adult has been largely confined to sodium chloride solutions, or to sodium lactate²¹ or sodium acetate solutions. Normal or isotonic saline is occasionally replaced by more concentrated solutions of salt, up to 5 per cent, for rapid replenishment of sodium and chloride in a small volume. These hypertonic solutions, however, may cause thrombosis of the vein used for the infusion. Sodium lactate or sodium acetate is generally given in isotonic $\frac{1}{6}$ molar concentration to provide sodium without chloride, the lactate or acetate being metabolized.

Recently, the importance of intracellular as well as extracellular electrolyte losses has been stressed.⁵ Potassium is the main intracellular constituent to be considered but the point at which there is need for its replacement after loss is still under investigation. Similarly, the significance of various

other electrolytes in parenteral nutrition remains to be established.

The administration of electrolytes should be carefully controlled. Edema follows excess of sodium chloride. This retention of salt may be promoted by renal injury. It may also occur after operation^{22,23} due, perhaps, to increased adrenal cortical activity²⁴ or to increased transudation of fluid into the interstitial space²⁵ as a result of diminished osmotic pressure consequent to hypoproteinemia.²⁶ Besides causing edema, saline infusions may lead to a transient increase in blood volume and consequent congestive failure in precariously compensated patients.²⁷

Excess of potassium is much more poorly tolerated. Changes found in the electrocardiogram or even cardiac arrest²⁸ may result from an elevated blood level of this anion.

Carbohydrate. The most physiologic source of carbohydrate for parenteral use is dextrose. A 5 per cent solution is customarily used. This concentration is isotonic and is not apt to introduce the dextrose at a faster rate than it can be cleared from the blood (0.8 to 0.9 Gm./Kg. body weight). Otherwise, hyperglycemia results with loss of sugar in the urine. A 5 per cent solution in normal saline is also in common use and is apparently not hypertonic enough to cause venous thrombosis (or cellulitis after subcutaneous use).

Ten per cent solutions of dextrose are definitely hypertonic and can only be given intravenously. Venous thrombosis and significant glycosuria may result.

Fat. Use of fat emulsions for intravenous administration⁶⁻⁸ is still in the experimental stage. There is an inherent danger of fat embolism from such mixtures. Blockage of the capillaries may result from insufficiently fine or unstable emulsification, and there may be overloading of the reticuloendothelial system. There is also a possibility of saturating the liver cells with fat.

Protein. 1. *Available Materials.* Gelatin can be given intravenously to combat shock

by the immediate restoration of blood volume. Whole human plasma proteins can be given intravenously for the same purpose but may be used also for nutrition. Being proteins they exert strong effects on osmotic pressure and blood volume. Human plasma, whole blood or serum albumin are the agents used.

A less expensive and less dangerous method of providing protein for nutrition is to furnish the amino acid precursors of protein for synthesis into protein by the body. These are obtained by the hydrolysis of a protein or by synthetic mixtures of amino acids. Since these materials must be reconstituted into protein, the parent protein must have been adequate in itself to meet the protein requirements of the animal organism. This adequacy is reflected chemically by the content of the ten essential amino acids.²⁹⁻³¹ It is reflected physiologically by the maintenance of growth³² and of nitrogen balance³³ when the protein in question is given as the sole source of nitrogen in the diet.

Casein, hydrolysed by either enzymes or acids, is the parent protein usually employed because of its high biologic value, ready availability and relatively low cost. The commercial product for intravenous use consists almost entirely of the component amino acids although small amounts of polypeptides may remain. These latter tend to limit tolerance and speed of administration. It is not clear whether these larger fragments are essential to man.^{32,34,35} Studies with the ten essential amino acids and glycine as the sole source of nitrogen have shown that nitrogen balance can be maintained in humans¹² without the presence of larger fragments. However, these experiments have been for short periods only and latent deficiencies may not have been revealed. Acid hydrolysis of casein destroys tryptophane which must be restored to such preparations.

Recently casein hydrolysates have been produced containing practically nothing but amino acids.^{36,37} These solutions are tolerated at speeds of infusion similar to

those at which glucose is given. This type of amino acid solution contains only the levorotatory forms of the amino acids. This provides an advantage over synthetic amino acid mixtures which consist of mixtures of equal amounts of the levo- and dextro-rotatory forms. The dextro-isomers are usually inactive physiologically and are not available for synthesis into protein.

Since the hydrolysate and amino acid mixtures must be acted upon to form tissue and serum proteins, the body mechanisms for this purpose must be intact. The liver is the principal organ concerned with deamination of amino acids and the synthesis of serum albumin. Thus, cirrhosis or acute hepatitis may result in hypoalbuminemia despite an adequate caloric and protein intake by mouth.³⁸ Food protein is hydrolyzed in the gastrointestinal tract and arrives at the liver essentially as an hydrolysate. Synthesis of albumin by the diseased liver is then inadequate to replace the daily loss of this protein, and parenteral hydrolysates are similarly ineffective. Their administration, then, will result either in their excretion in the urine, or diffusion into tissue spaces or accumulation in the blood with the induction of nausea.^{12,39} Hypoproteinemia, that is hypoalbuminemia, under these circumstances may be combatted by the use of preformed protein intravenously. This is now possible with whole blood plasma or human albumin.⁴⁰

Serum proteins are thought to be in equilibrium with tissue proteins.⁴¹ Weech et al.⁴² have postulated from experiments with malnutrition in dogs that 30 Gm. of tissue protein are burned by the body to 1 Gm. of serum protein. During anabolism, or protein replenishment, the same partitioning of protein between tissue and serum occurs.⁴³ Thus, as an approximation, if the same ratio holds in man the infusion of 500 cc. of plasma containing 6 per cent protein (30 Gm.) can provide only 1 Gm. of serum protein for the circulation. The rest can be expected to enter the tissues. This 1 Gm. of serum protein divided by an approximate plasma volume of 2,500 cc.

would provide a sustained rise of only about 0.04 Gm. protein per cent.

The slow rise in serum protein titer after plasma infusions and the disappearance from the circulation of the greater part of the infused protein are well known^{40,44-47} although the effects upon blood volume of complicating factors such as administered fluids, altered renal or circulatory functions and preceding hemorrhage must be taken into account in any such evaluation. The rate of disappearance of serum proteins from the blood stream diminishes as tissue stores are replenished. Also, the rate of protein synthesis becomes increased. This problem has been extensively studied by Whipple and his group in dogs subjected to plasmapheresis.¹⁹ Hemoglobin also is thought to be in equilibrium with the other proteins of the body; thus the provision of whole blood will spare considerable amounts of tissue and serum proteins which would be drawn upon to synthesize red cells and hemoglobin in the replacement of blood loss.

To estimate the loss or gain of nitrogen it is necessary to determine the nitrogen balance. Retention of nitrogen in significant amounts occurs only during the growing period or following nitrogen loss. Such a loss may result from inanition,¹⁶ hemorrhage,⁴¹ suppuration, wound or skin ooze such as occurs after burns.⁴⁸ Disease or trauma tends to initiate a sharp negative nitrogen balance⁴⁹ during which period nitrogen storage is difficult to achieve. The degree of nitrogen loss is more or less in proportion to the extent of the injury.^{50,51} The tendency to lose nitrogen during the immediate post-traumatic period may be overcome by a high intake of nitrogen^{11,12} or of calories and nitrogen,⁵² but positive nitrogen balance cannot generally be achieved until the later recovery period. A possible explanation, among others,^{24,49} for this failure may be found in the inability to administer sufficient calories, with the nitrogen, to the sick and often febrile patient. This problem of calories in relation to nitrogen balance will be discussed later.

Nitrogen balance studies reveal a tremendous difference in the ease with which nitrogen given as preformed plasma or red cell protein provides a positive balance as compared with nitrogen given as split protein in the form of hydrolysate or amino acids.¹⁵ The difference is accounted for by the increased excretion of nitrogen with the latter. This same rise in urinary nitrogen appears in the dog when serum protein and whole blood are given by mouth; the urinary nitrogen level rapidly increases which does not occur when the same materials are given by vein.⁵³ The mechanisms for handling split and whole proteins thus differ in important respects.

Fed protein is hydrolyzed in the gastrointestinal tract and must be acted upon by the liver before entering the blood stream. There is, apparently, considerable waste involved in deamination and subsequent handling of these amino acids by the liver. Preformed protein given by vein is not directly acted upon by the enzyme systems of the liver and does not appear in the urine as urea until long after its administration.⁵⁴ This lag in excretion and greater efficiency of utilization results in a more positive nitrogen balance than can be obtained with amino acid mixtures.

The amino acid mixtures, on the other hand, have an advantage over serum protein for the patient in regard to the intermediary metabolism of nitrogenous substances. In the experimental animal it has been demonstrated that the provision of amino acids to the liver is essential for the maintenance of normal liver function.⁵⁵ The lipotropic action of these substances, especially methionine,⁵⁶ is not obtained with preformed serum protein. Thus, the fatty liver of starvation is prevented or alleviated by food protein by mouth or by parenteral hydrolysates but not by intravenous blood or plasma. Varco⁵⁷ has emphasized the failure of blood or plasma alone to prevent mortality in this group following operation. Autopsy showed fatty livers in his badly starved patients treated only with transfusions. Kremen has advocated the use of

both hydrolysate (or amino acid) mixtures and serum protein to achieve positive nitrogen balance and to provide a substrate for liver activity.

2. *Calories.* Protein without fat or carbohydrate is not adequate for nutrition. Rats on a pure protein diet will soon succumb.⁵⁸ This toxicity can be prevented by carbohydrate which also serves to spare nitrogen to the body. Butler et al.⁵⁹ have studied the minimal carbohydrate requirement to spare nitrogen and place this figure at 100 Gm. of glucose. Elman and associates⁶⁰ have reported that calories are relatively unimportant inasmuch as nitrogen equilibrium can be achieved in the dog by increasing the intake of an hydrolysate despite a low caloric diet. About the same time¹² it was demonstrated that increasing the level of nitrogen intake could maintain nitrogen equilibrium in the human despite accompanying low calories. The latter study was complicated by the possibility that previous nitrogen depletion had been a factor, and by the complications introduced by operation.

This problem has been pursued further⁶¹ in the presumably non-depleted healthy and uninjured subject. In this group the intake of calories was sharply reduced after a baseline period, and this was found to result in a markedly negative nitrogen balance despite maintenance of the previous protein intake. Similarly, a sudden reduction in protein without alteration in calories, or reduction of both protein and calories, caused a loss of nitrogen. The degree of negative balance was equal to that seen after many operations or trauma. Thus reduction in caloric and protein intake after injury, plus the added demands for both during the febrile period, probably explains in large part the so-called "catabolic response" to injury. A considerable increase in administered nitrogen over that given in the control period restores nitrogen equilibrium despite reduction in calories. This reduplicates the experience with post-operative patients. These observations clearly indicate that provision of both

calories and nitrogen is desirable in any nutritional effort.

To furnish these added calories parenterally, glucose must be given with the nitrogenous solutions and at concentrations approaching isotonicity. The achievement

volumes indicated are in excess of the amount that can safely be given intravenously even with the help of hypodermoclyses and of rectal taps of glucose or of glucose in saline. Therefore, Elman has attempted to compromise by providing

TABLE I

COMPARISON OF FLUID VOLUMES NECESSARY TO PROVIDE 1,200 AND 1,800 CALORIES WITH 90 GM. PROTEIN INTAKE AND ADEQUATE SALT, USING HYDROLYSATE OR AMINO ACID SOLUTIONS

Preparation	Glucose Gm./L.	Protein Equivalent Gm./L.	Salt Gm./L.	Calories/L.	Liters of Fluid	
					1,200 Calories	1,800 Calories
90 Gm. Protein						
Casein hydrolysate 5% } Dextrose 5% Dextrose 5%	50 50	37.5 0	2 0	350 200	2.5 1.6	2.5 4.6
					Total 4.1	Total 7.1
Amino acids 10% Dextrose 5% in saline Dextrose 5%	0 50 50	80 0 0	0 8.5 0	320 200 200	1.1 1.0 3.2	1.1 1.0 3.2
					Total 5.3	Total 8.3
Casein hydrolysate 5% } Dextrose 5% Dextrose 10%	50 100	37.5 0	2 0	350 400	2.5 0.8	2.5 2.3
					Total 3.3	Total 4.8
Amino acids 10% Dextrose 5% in saline Dextrose 10%	0 50 100	80 0 0	0 8 0	320 200 400	1.1 1.0 1.6	1.1 1.0 3.1
					Total 3.7	Total 5.2

of adequate caloric intake thus requires a large ultimate total fluid volume, a matter of major importance. The accompanying tables summarize this problem. Table I indicates the fluid volumes involved in supplying the equivalent of 90 Gm. of protein, salt, and either 1,200 or 1,800 calories in terms of a 5 per cent hydrolysate-5 per cent dextrose solution and a 10 per cent hydrolysate or amino acid solution with supplementary glucose. Table II shows similar volumes at the same caloric intake but with the provision of somewhat more protein equivalent. Most of the

only 100 Gm. of glucose and 100 Gm. of hydrolysate or amino acid solution per day, equivalent to about 75 Gm. of protein and 700 calories, during parenteral feeding. His attainment of nitrogen equilibrium with this regimen has not been confirmed by the writer in most instances^{12,61} although the provision of considerably more nitrogen than recommended by Elman, the equivalent of about 160 Gm. of protein and about 1,000 to 1,200 calories, was found to achieve this result.

3. *Complications.* In any event, cardiac and renal functions must be adequate in order

to tolerate most intravenous therapy. Otherwise heart failure may occur during treatment. This is especially true of older patients in whom a diminished cardiac reserve often exists, sometimes undetected. The stress of infusion may then precipitate

other fluids. It is the expanded blood volume which causes increased cardiac work and hence may exhaust an already diminished cardiac reserve.

By the administration of fluids through a venous pressure machine and the deter-

TABLE II
COMPARISON OF FLUID VOLUMES NECESSARY TO PROVIDE 1,200 AND 1,800 CALORIES WITH 120 AND 200 GM. PROTEIN INTAKES AND ADEQUATE SALT, USING HYDROLYSATE OR AMINO ACID SOLUTIONS

Preparation	Glucose Gm./L.	Protein Equivalent Gm./L.	Salt Gm./L.	Calories/L.	Liters of Fluid	
					1,200 Calories	1,800 Calories
120 Gms. Protein						
Casein hydrolysate 5% } Dextrose 5% }	50	37.5	2	350	3.5	
Amino acids 10%.....	0	80	0	320	1.5	
Dextrose 5% in saline.....	50	0	8.5	200	1.0	
Dextrose 5%.....	50	0	0	200	2.6	
					Total 5.1	
Amino acids 10%.....	0	80	0	320	1.5	
Dextrose 5% in saline.....	50	0	8.5	200	1.0	
Dextrose 10%.....	100	0	0	400	1.3	
					Total 3.8	
200 Gm. Protein						
Casein hydrolysate 5% } Dextrose 5% }	50	37.5	2	350	...	5.2
Amino acids 10%.....	0	80	0	320	...	2.5
Dextrose 5% in saline.....	50	0	8.5	200	...	1.0
Dextrose 5%.....	50	0	0	200	...	4.0
						Total 7.5
Amino acids 10%.....	0	80	0	320	...	2.5
Dextrose 5% in saline.....	50	0	8.5	200	...	1.0
Dextrose 10%.....	100	0	0	400	...	2.0
						Total 5.5

right or left heart failure or both. Plasma proteins are especially dangerous in this respect since they are not as rapidly removed from the blood stream after infusion as are saline solutions and glucose; the increase in blood volume produced by their introduction into the circulation is more persistent than that caused by these

mination of vital capacity⁶² during infusion objective evidence of heart failure may be obtained before the appearance of symptoms. The determination of blood volume also gives an index of the circulatory load. By judicious control⁶³ one may avoid administration of additional fluid to a patient with an already overexpanded

circulating volume. To disregard these precautions or to fail to evaluate cardiac and renal function by history, physical examination and objective methods before resorting to parenteral therapy may result in pulmonary edema and even death.

Other determinations, such as estimation of the hematocrit or serum proteins may reveal hemodilution. Such dilution must be interpreted in terms of recent blood loss, variations in plasma protein synthesis and water balance. The daily weight, fluid intake and output, and blood urea or non-protein nitrogen values can also be followed as safeguards against overinfusion. A rise in blood urea nitrogen during hydrolysate therapy may, however, result from metabolism of the amino acids¹² rather than from renal injury. This rise is comparable to the one which may follow ingestion of large quantities of meat.⁶⁴

Apart from the aforementioned circulatory considerations, the requirements for rest and the problem of available veins may create difficulties in the timing of the administration of parenteral fluids. Repeated infusions permit the patient to become ambulatory or to rest in the interim periods. Unfortunately, available veins soon disappear. Some type of continuous infusion or of indwelling plastic catheter is necessary for more than brief feeding programs. The advantages of this method with its single venipuncture and its freedom of mobility for the patient are counterbalanced by the high incidence of local venous thrombosis. This is apt to occur after several days or less. Thrombosis of the vein proximal to the point of introduction of the needle or catheter may result from irritation of the intima of the vein by the infusion fluids. This can be avoided by release of the fluid into the vein with a sufficiently large blood flow to provide immediate dilution. The plastic catheter makes available the upper brachial or axillary veins which meet this requirement. Previous thrombosis of the tributaries, however, may reduce the blood flow enough to permit thrombosis of even these larger vessels.

Reactions to parenteral fluids are few. Removal of pyrogens, treatment of infusion tubing with sodium hydroxide after infusion of organic materials such as blood and hydrolysates, or use of a new plastic tubing with each infusion have practically eliminated complications. However, nausea and vomiting may result from too rapid infusion of hydrolysate or amino acid solutions.^{12,98} This reaction cannot be too well correlated with the level of blood amino acid³⁹ in the author's experience.¹² Rest periods between infusions and the introduction of not more than 50 Gm. of amino acid mixture at one time avoid this complication. Shock-like responses to the larger molecules in the less purified hydrolysates may occur and are avoided by a slow rate of administration.

The avoidance of transfusion reactions by proper cross matching and the development of urticaria from too rapid plasma or blood infusions need no discussion here. Homologous serum jaundice is another complication of preformed serum protein therapy with whole blood or plasma.

The excellence of nitrogenous materials as culture media makes strict precautions for sterility necessary. Unused but opened solutions should be discarded and not saved for later use. Apart from contamination these solutions may occasionally cloud or precipitate spontaneously; they should not be given if this occurs.

COMMENTS

The requirements for concomitant calories, the volume of fluid needed, the technics of administration and the dangers and problems inherent in giving such fluids parenterally have been reviewed. The value of this type of nutrition requires further discussion.

It was pointed out elsewhere⁴¹ that the body has stored or dispensable nitrogen that can be called upon in a crisis without apparent ill effect. This nitrogen is thought to be intracellular, there being no specific depots for nitrogen as there are for fat. Since brief periods of starvation produce no demonstrable difficulties in non-depleted

subjects as shown by their behavior after injury or operation when no special efforts at feeding are made, it would appear that there is no need for parenteral nourishment in this group. However, after prolonged periods of undernutrition the existing depletion of nitrogen stores may lead to hypoproteinemia due to inability to meet the increased demands for nitrogen associated with operation.

Replenishment of protein stores is obviously desirable in these depleted patients. Experience with high protein intakes indicates that this is more readily accomplished before operation since more nitrogen may be stored from a given amount of protein nitrogen before than after surgery. The oral route should be employed under these circumstances since parenteral administration does not generally result in retention of nitrogen. The rationale for employing parenteral nutrition when oral feeding is not available prior to operation presumably rests more on the restoration of liver function⁵⁷ and on the effects of adaptation to a more vigorous nitrogen turnover^{5,61} than on storage of nitrogen. The amounts of nitrogen retained during such treatment are limited due largely to the inadequate provision of calories. This type of therapy, however, is probably justified, especially in conjunction with plasma or whole blood,¹⁵ although only for a short period preoperatively since rapid weight loss, as well as poor nitrogen retention, may result from inadequate calories.

In the postoperative period, parenteral nitrogen therapy is intended to lessen nitrogen loss. This can be accomplished although, again, nitrogen retention cannot be expected in the face of the provision of low calories and of increased demand. Thus, such therapy will not necessarily prevent hypoproteinemia.

It should be pointed out that administration of high nitrogen levels parenterally, once begun either before or after operation, should be continued during the first few days after operation. Otherwise, the sudden discontinuance or reduction of the nitrogen

intake for one or two days may result in sharp nitrogen losses due to the fact that the nitrogen excretion continues at the same level as if the high intake had continued. A loss to the body of 20 to 30 Gm. of nitrogen in a single day may thus result. (Fig. 1.)

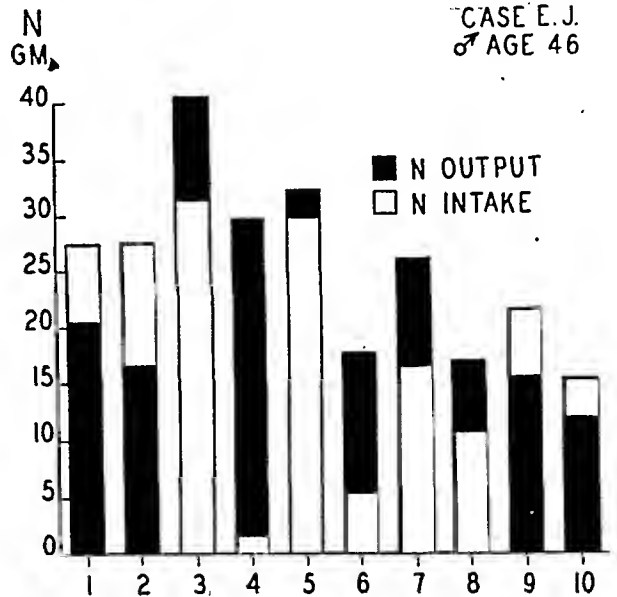


FIG. 1. Showing sharp loss of nitrogen following interruption of amino acid therapy by vein in the postoperative period after subtotal gastrectomy. (WERNER, S. C. *Ann. Surg.*, 126: 180, 1947.)

This loss may be minimized in the later postoperative period when the patient can ingest adequate amounts of food protein and calories to compensate for a reduced intake by vein.

If postoperative therapy appears indicated for the reasons just discussed, the question then arises as to what benefit results in actual clinical experience. In the observations made at the Presbyterian Hospital it was not possible to prove betterment beyond question.¹² Twenty-five patients undergoing subtotal gastrectomy for peptic ulcer were compared with fifty patients handled identically, except that the latter received no parenteral nitrogen postoperatively. Such a comparison in respect to benefit from parenteral nitrogen therapy after operation is admittedly difficult due to lack of objective criteria.

Nitrogen was spared the amino acid-treated patient as compared with the controls, judged from nitrogen balance de-

terminations. Clinically, one-third of the control patients suffered some complication, possibly, but not unquestionably, attributable to the consequences of hypoproteincemia. The remaining two-thirds of the control patients behaved in every way as did the group given parenteral nitrogen; they ate a full diet, had a subsidence of temperature and left the hospital after the same interval as did the treated patients. Thus, the difference between the two groups, in terms of clinical benefit, is suggestive only and is not conclusive.

It may be proven by more extensive experience that postoperative nitrogen administration will prevent the complications which afflicted one-third of the control group. The use of such materials would then be indicated in all operated patients since one cannot predict in which case a complication will develop.

One cannot help but wonder if the use of hydrolysate and amino acid by vein should not be limited first, to those postoperative cases in which previous protein depletion has occurred and has not been replenished preoperatively; second, to those in which evidence of a postoperative complication already has appeared.

CONCLUSION

Critically controlled observations are still needed to evaluate the proper place of parenteral hydrolysate and amino acid therapy in man.

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Amino Acid Mixtures as Parenteral Protein Food*

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SOLUTIONS containing amino acid mixtures have been established as a means of giving protein food parenterally. The present paper aims to summarize the literature on its use during the years 1945, 1946 and 1947. Reports previous to 1945 have been discussed elsewhere.¹⁸ In reviewing the fairly large bibliography which has developed on the parenteral use of amino acid mixtures only reports containing objective data were selected.

Terminology. Considerable confusion exists as to terminology because many preparations contain only amino acids, others amino acids and peptides; moreover, those containing only amino acids may either be mixtures of the pure crystalline material or completely hydrolyzed protein. While no simple, all inclusive term seems satisfactory, the author prefers to use amino acid mixtures to include both the pure crystalline material on the one hand as well as protein hydrolysates (or digests) on the other. This is similar to the generic term amino acid preparations used in the 1947 edition of *New and Non-Official Remedies*⁴⁹ to apply to the two protein hydrolysates described. The word peptide might be added, i.e., amino acid and peptide mixtures, except that it detracts from simplicity. Moreover, all preparations containing peptides also contain amino acids; it would seem that the term mixture should include peptides as well as other substances present.

The term amino acid mixture is preferable to the term protein hydrolysate, in that the latter may be applied to protein

which has been only slightly digested and therefore designed to be injected not as a source of protein food but as a colloidal solution. For example, solutions of gelatin, although used for their colloidal effect, are always hydrolyzed since the extraction with boiling water from tissues leads to considerable splitting of the molecule at peptide linkages. Several preparations examined by the author contained as much as 4 to 6 per cent of the nitrogen as free amino acids. Federov²⁰ prepared a weakly hydrolyzed casein in order to render it non-antigenic so that it could be used for its colloidal effect. Brinkman et al.⁴ described a more extensively broken down casein hydrolysate in which there was a sufficient concentration of large particles to exert a definite colloidal effect and yet contained enough free amino acids and small peptides to serve as a source of parenteral protein food. Thus, the term protein hydrolysate can be applied to preparations in which the digestion has had purposes other than the production of amino acids or small peptides for nitrogenous nourishment. It should be emphasized that the term amino acid mixture is used only for this general discussion of the subject; when applied to the sale of preparations for clinical use, other considerations apply.

VARIETIES OF AMINO ACID MIXTURES

A number of different amino acid mixtures have been described in the literature in a variety of ways. It is often difficult to know just what kind of preparation is being used inasmuch as the published details are

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often scanty. With this in mind, an attempt will be made in the following discussion to describe the various preparations. A brief summary is also presented in Table 1. It should be emphasized that only preparations designed for parenteral use will be considered.

An amino acid mixture prepared from pure crystalline material was first injected in 1940 by Shohl and Blackfan.⁵⁶ Subsequent to this Madden and his co-workers examined the effect of various pure mixtures in the regeneration of serum protein in depleted dogs⁴⁶ and in humans.⁴⁷ Both groups of investigators used solutions made up with single amino acids put together in various proportions. Shohl and Blackfan used a mixture matching as closely as possible the composition of casein; Madden and his co-workers employed mostly essential amino acids plus glycine. Many of the single amino acids were synthetic and available only in the racemic form so that the final preparation often contained a fairly large proportion, up to 20 per cent or more, of the constituent amino acids in the unnatural form. Madden and his co-workers employed many different mixtures but most of the observations subsequently were made with the so-called vuj mixtures. The most extensive study in the human with the vuj mixture of crystalline amino acids was carried out by Werner,⁶⁸ who observed the effect of this solution when injected intravenously in a total of seventy-three patients.

Of the amino acid mixtures prepared from protein hydrolysates, the enzymic casein hydrolysate amigen, and the acid casein hydrolysate fortified with tryptophane parenamine have been described previously.¹⁸ A number of other hydrolysates have been prepared and studied in the past three years. White and Weinstein,⁷⁰ in a group of forty-nine surgical patients, injected intravenously 200 L. of a 6 per cent protein hydrolysate which was described merely as "an enzymatic digest of mammalian protein." Extensive studies have also been made with a partial acid hydrolysate of casein and of fibrin, prepared by the

method described by White and Elman.⁶⁹ Studies with this preparation have been reported in animals by Risser and his co-workers⁵³ Frost and his co-workers²³⁻²⁵ and in humans by Koop et al.^{36,37} This type of acid hydrolysate differs from previous

TABLE 1

VARIOUS AMINO ACID MIXTURES INJECTED INTRAVENOUSLY	
Type of amino acid mixture	Name
Crystalline amino acids.....	VUJ
Crystalline amino acids.....	VU
Enzymic casein hydrolysate.....	Amigen
Complete fortified acid casein hydrolysate.....	Parcnamine
Enzymic hydrolysate mammalian protein	
Partial acid hydrolysate of fibrin and casein.....	Aminosol
Enzymic dialyzed casein hydrolysate....	Aminosol
Papain pork hydrolysate.....	
Lyophilized acid casein hydrolysate.....	Baxter
Partial (fortified) acid casein hydrolysate....	
Acid hydrolysate of fish protein.....	Cutter
Complete fortified casein hydrolysate (glutamic and aspartic acid removed).....	

preparations in that the degree of hydrolysis is not complete so that peptides are present, the proportion of which may vary within certain limits. This partial acid hydrolysate of fibrin has been called aminosol by the manufacturer. However, the same word has been applied to a Swedish product by Wretling,^{72,73} and by Goldberg and Wretling.²⁷ The latter product was made by first digesting casein with trypsin and erepsin and then dialyzing the solution to rid it of larger particles. It has been used in animals and in humans. Several partial acid hydrolysates prepared according to the method of White and Elman⁶⁹ in which pure amino acids have been added have also been described by Sahyun⁵⁵ and employed in animal studies. An amino acid mixture described merely as a "Baxter product" was given intravenously to a patient with ulcerative colitis by Remington et al.,⁵² with excellent clinical effect. Kozoll et al.³⁹ injected in four patients with upper intestinal obstruction a product made by Cutter by the acid hydrolysis of fish protein.

A papain digest of animal protein was described rather briefly in a report by Basu;^{1,2} it was apparently similar to the papain digest previously reported by Krish-

nan⁴⁰ made by hydrolyzing pork. The same preparation was also used by Viswanathan⁶⁶ in patients with hepatitis and the process of hydrolysis described more fully. Hoffman and his co-workers³¹ and Kozoll and Mok³⁸ injected an acid casein digest in which some of the aspartic and glutamic acids had been removed and the product finally lyophilized. Perhaps similar to this is a brief report by Eckhardt et al.¹⁶ who described a complete acid digest of casein rendered free of aspartic and glutamic acids to which tryptophane, methionine and glycine were added.

Variations in Amino Acid Mixtures. Amino acid mixtures may vary in many ways, entirely apart from their relative composition of amino acids and peptides. First is the presence of substances, not amino acids or peptides, which remain during the preparation of any solution of hydrolyzed protein. Some of these substances are really impurities which have resisted attempts at removal and may be responsible for some of the reactions which follow their entrance into the blood stream. Other substances may be of nutritional value insofar as food protein may contain as yet unknown constituents other than amino acids. Crystalline amino acid mixtures, of course, should contain no material of this sort if the individual acids have been adequately purified.

Variations may also occur in the pH of solutions of amino acid mixtures, depending upon the type of preparation but also upon the proportion of the various amino acids present. The isoelectric point of amino acids varies; many are acid and others are alkaline, depending largely upon the presence of one or two free amino or carboxyl radicals. The pH of an intravenously injected solution of amino acids is much more important than that of glucose because the former is such an excellent buffer. Solutions of amino acids which are very far from the neutral point may therefore have a significant influence on the acid base balance. Such solutions can, of course, be neutralized by adding a mineral acid or base, but this may lead to difficulty since the amino acid portion is rapidly metabolized, leaving a

free acid or base in the body. On theoretical grounds it would seem that a proper mixture of basic and acidic amino acids would be the best way of preparing a neutral solution.

The electrolyte composition of amino acid mixtures may also vary greatly. For example, hydrolysates prepared from animal cells will contain much potassium and magnesium; the pork digest of Krishnan⁴⁰ must certainly be rich in these salts which are largely the sole intracellular electrolyte. Fibrin and casein, on the other hand, being extracellular proteins will contain relatively little salt, mostly sodium. As far as soluble salts are concerned the final electrolyte composition of electrolyte is of more than academic interest. In surgical patients, for example, too much sodium chloride may be harmful when not needed. On the other hand, some salt is always necessary. The need for potassium and magnesium is not yet established, but further study may show that it plays an important part in the synthesis of intracellular protein from amino acids and peptides.

REACTIONS FOLLOWING INTRAVENOUS INJECTION

In spite of much study there is some confusion in the literature as to the cause or causes of the various reactions which may follow an intravenous injection of amino acid mixtures. However, the use of these solutions is now so extensive that serious or frequent reactions are largely a thing of the past.

Nausea and Vomiting. There is general agreement that certain solutions containing only the essential amino acids plus glycine in crystalline form can be given to humans at very much more rapid rates without the production of nausea and vomiting than is the case with solutions of hydrolyzed protein. This observation was first made by Madden and his co-workers⁴⁷ and confirmed by many others since then.^{17,61,68} Of the specific amino acids, glutamic and aspartic acids were first shown to be responsible for nausea and vomiting in dogs by Madden et al.⁴⁴ Smyth et al.⁶² confirmed

these observations in humans. In both studies the glutamic acid solution was neutralized with sodium bicarbonate and sterilized by heat. On the other hand, the present author¹⁷ injected unneutralized glutamic acid sterilized by heat in three patients without any evidence of reaction. It would seem that pH and heat have an effect upon the emetic properties of this amino acid perhaps by its conversion to pyrrolidonecarboxylic acid. The observations recorded by Werner⁶⁸ should be mentioned in connection with reactions following the intravenous injection of amino acid mixtures. This worker found that a solution of the vuj crystalline amino acid mixture at pH 5.5, if neutralized, provoked nausea and vomiting even when injected in small amounts. Roth et al.⁵⁴ confirmed the emetic effect of glutamic acid in dogs with a solution prepared by dissolving the natural unneutralized amino acid in a 5 per cent solution producing a pH of 1.1. No mention was made as to whether the solution was sterilized by heat. They found that the average dose which produced vomiting on intravenous injection was 136 mg. per Kg. of body weight. Nembutal improved the tolerance by 84 per cent, epinephrine by 45 per cent; however, the tolerance was increased on repeated injections four to six days later. Unna et al.⁶⁵ injected neutralized 2 per cent glutamic acid and also aspartic acid intravenously in dogs and found that both produced emesis which was not improved by the addition of glycine. Whether or not the solution was sterilized by heat was not stated.

The probable influence of aspartic and glutamic acid on nausea and vomiting in the human was described in a brief preliminary report by Eckhardt et al.,¹⁶ in that a 10 per cent solution of a complete acid hydrolysate of casein was used in which these two amino acids were said to be completely removed and tryptophane, methionine and glycine added. The solution was given at a very rapid rate, 500 cc. in ten or fifteen minutes. Only rarely was vomiting observed and only one-fourth of

the patients had nausea. At one hour even nausea was rare. No thrombosis was noted. The method of preparation of the solution was not described.

That nausea and vomiting may be caused by unnatural amino acids was shown by Howe et al.³⁴ in very carefully controlled observations in dogs. They found that the racemic form, especially methionine, was responsible for considerable nausea and vomiting and that glycine neutralized this effect. This would explain the observation of Madden and his co-workers⁴⁴ that the addition of glycine improved the tolerance of crystalline mixtures of essential amino acids. Howe and his co-workers³⁴ found that the monoamino and monocarboxylic amino acids produced no nausea or vomiting when injected at a rate of 5 to 22 mg. of nitrogen per Kg. per minute. However, the same amino acids in the racemic form produced repeated vomiting even when given at a rate of 1 to 2 mg. of nitrogen per Kg. per minute. A mixture of nine natural essential amino acids could be given at a rate of 20 to 35 mg., yet only two of nine were followed by vomiting. This careful study it would seem indicates that, in the dog at least, the unnatural forms of amino acids may produce severe nausea and vomiting. These conclusions have been previously reached by Cox et al.¹⁰ although no detailed evidence was presented.

Other Reactions. Many observations have been made of the tolerance to intravenous injections of various amino acid mixtures. One of the most extensive studies was carried out by Hecht³⁰ who injected 500 cc. of parenamine in saline, in glucose or in glucosc-saline at a concentration of 1.5 to 7 per cent 550 times in 303 patients. There were twenty-two reactions or an incidence of 4 per cent. However, in only 1.3 per cent of the injections did the infusion have to be discontinued. The twenty-two reactions were classified as follows: chills and/or fever, eight times; nausea and vomiting, eight; headache, two; dyspnea, two; precordial and lumbar pain, one each. No reaction was alarming. Smyth and his co-

workers⁶³ compared the effect of parenamine, of amigen and of a crystalline mixture of amino acids in eight patients. Parenamine, after a dose of 15 Gm. injected during two hours, produced relatively severe symptoms such as dizziness, nausea, vomiting, anorexia and weakness as compared with a similar dose of amigen. In a subsequent study by the same authors,^{59,60} parenamine was found to produce pronounced depression in appetite as compared with amigen. Crystalline amino acid mixtures had no effect whatever on appetite and was tolerated best of all in that it could be given at a much more rapid rate than the other two preparations without producing symptoms. Werner⁶⁸ gave 350 infusions of crystalline amino acids in an 8 per cent solution at a maximum rate of injection of 400 cc. per hour. There was no nausea or vomiting and only five patients had pyrogenic reactions. A study by Winbury and Crittenden¹⁷ is of interest in showing some of the deleterious effects following the intravenous injection of amino acids, but the doses used were so high that they probably had very little clinical significance. An attempt to study the sensitivity of humans to various preparations of hydrolyzed proteins as a guide to the safety of intravenous injections was made by Ficarra²¹ who used an intradermal test. The author found that patients will react to one product but not to another. However, no data were reported.

The dialyzed casein digest described by Goldberg and Wretling²⁷ was injected in doses of 500 cc. of a 3.3 per cent solution intravenously to 2 Kg. rabbits with no harmful effects. The tolerance to the injection in mice was greater than in guinea pigs and rabbits. Using a 26 per cent solution, rabbits required 6 to 24 Gm. per Kg. before a fatal outcome was produced. These, of course, are tremendous doses and one wonders whether the effect was not due to the abnormally large volume of fluid injected rather than to its content of protein hydrolysate. The injections used would be equivalent to giving 15 to 52 L. to a 70 Kg. man. The clinical use of this digest in

moderate doses had provoked no untoward effects.^{72,73}

Curreri et al.¹⁴ described a fatality following the intravenous injection of an amino acid mixture (amigen). Although the cause was not established, most of the data would suggest that a highly contaminated solution was responsible.

METABOLISM OF INTRAVENOUSLY INJECTED AMINO ACID MIXTURES

During the past three years a number of metabolic studies have been carried out following the intravenous injection of amino acid mixtures.

Urinary Excretion of Amino Acids or Peptides. Risser and his co-workers⁵³ found in control observations in animals on a normal oral protein intake that 3 to 9 per cent of the total urinary nitrogen was amino acid nitrogen. However, if the urine was hydrolyzed with acid, the value for amino acid nitrogen was doubled, indicating the excretion of polypeptides. It is obviously important to measure the excretion of both amino acids and polypeptides in the urine, particularly when partial protein hydrolysates containing peptides are injected. Risser and his co-workers found that the injection of a partial hydrolysate, 75 to 83 per cent of the nitrogen of which is present as peptides, produced just as an effective nitrogen balance as a complete hydrolysate given at the same minimal level of 120 mg. of nitrogen per Kg. per day, in spite of the fact that there was a large excretion of peptides and amino acids with the partial hydrolysate. This would seem to indicate that something was present in the retained part of the partial hydrolysate which improved nitrogen balance, inasmuch as the part not excreted could have maintained balance at a much lower level of intake. They also found that the excretion of peptides was greater with rapid injections, for example, 162 mg. of nitrogen per Kg. injected in thirty-five minutes resulted in the urinary loss of 15.5 per cent as amino acids and of 28.7 per cent as amino acids and peptides.

An important study of peptides in the urine as well as in the blood was carried out by Christensen and his co-workers⁸ using newer methods for the detection of peptides. They studied first of all the effect of intravenous amigen in humans. This enzymatic hydrolysate of casein produced a prolonged increase of blood peptides, but the free amino acid level promptly dropped to normal levels following the injection. However, 36 to 53 per cent of the peptides, in contrast with but 2.4 to 6 per cent of amino acid present in the original hydrolysate, appeared in the urine. The authors conclude, therefore, that the peptides of amigen appear to be less readily utilized by the tissues and more poorly retained by the kidneys than pure amino acids. Christensen⁹ in further studies compared the urinary loss and nitrogen balance of intravenous amigen with that of aminosol (partial acid hydrolysate of fibrin). First of all it was observed that with both products the disappearance curve in the blood of both amino acids and peptides, after intravenous injection, was about the same. Since aminosol contains twice as much peptide nitrogen as amigen, it was concluded that the peptides from the partial acid hydrolysate were more efficiently utilized than from the enzymatic hydrolysate. This was confirmed by the fact that only about 25 per cent of the peptides in aminosol was lost in the urine, in contrast to the higher figure of 40 per cent for peptide loss following the injection of amigen. It should be noted, however, that the magnitude of the nitrogen balance was identical for the two preparations. The dose used in these studies was 500 to 1,000 cc. containing 7.2 Gm. of nitrogen per L. In a footnote the authors describe an experimental preparation of aminosol in which the hydrolysis was carried further so that the peptide nitrogen content was similar to that of amigen; this product after injection was followed by a loss of only 10 to 18 per cent of its peptide nitrogen in the urine. Smyth et al.⁶¹ also observed in humans that as compared with parenamine and a mixture of crystalline amino acids, amigen was

followed by the largest excretion of amino acid nitrogen, most of it being peptide nitrogen amounting to 11 per cent of the amount injected. Werner⁶⁸ studied the urinary excretion of amino acids in fifteen humans following the intravenous injection of 80 to 240 Gm. of crystalline amino acids (vuj mixture). The amount lost in the urine was a very tiny percentage of the amount injected, i.e., 1 to 4 Gm. This is surprising in view of the fact that 14 per cent of the vuj mixture consisted of the unnatural forms. In a previous study by the author,¹⁷ in which a similar mixture of crystalline amino acids (vu) was injected, nearly all, or 20 per cent, of the unnatural amino acids appeared in the urine.

Other Studies. An interesting study of the fate of an acid hydrolysate of casein when injected into rats was carried out by Friedberg and Greenberg.²² Parenamine was injected (10 cc. in isotonic saline solution adjusted to a pH of 7.4 with sodium carbonate) at a rate of 0.16 Gm. of amino nitrogen per Kg. of body weight. The animals were killed fifteen minutes later and several amino acids measured in various parts of the body. It was found that 80 to 90 per cent of the amino acids had disappeared from the plasma. The liver and kidneys contained the greatest increases but that in the liver was much less. No increase was found in the brain. The authors found that normally the liver contains 32, the kidney 46, muscle 19, brain 43 and plasma merely 6.4 mg. per cent of amino nitrogen. This study confirms to a considerable extent the older observations made by Van Slyke and Meyer.

Hoffman et al.³² measured blood changes in thirty humans following the intravenous injection of parenamine in doses of 45 Gm. per L. given at the rate of 300 to 350 cc. per hour. The solution had a pH of 4.2. The maximum mean changes were an increase of +4.9 mg. of amino nitrogen when about one-half of the injection had been completed, and +6.6 in the non-protein nitrogen one hour following the injection. There was a fall in the phosphate of the

plasma amounting to but 0.5 mg. per cent at the middle of the injection, and a fall in the carbon dioxide combining power of 4 volumes per cent at the end of the injection. Werner,⁶⁸ using the vuj mixture of crystalline amino acids, found pronounced falls in the CO₂ combining power of the plasma after the injection of 3 L. of an 8 per cent solution, the values varying from 16 to 58 volumes per cent (controls 53 to 73). One fatal case was described in which a drop to 16 volumes per cent was observed. This worker found it necessary to provide sodium lactate as a base when large amounts of solutions were injected, presumably because the vuj mixture, when dissolved, had a pH of 5.5. Similar observations have not been made by others using this same preparation.

A study of the effect of intravenous amino acids on creatine was made by Grossman.²⁸ In four control patients given 50 Gm. of glucose as a 50 per cent solution intravenously there was no increase in the serum creatine although one had creatinuria. In twelve patients given 50 Gm. of amigen intravenously, either as a 10 or 5 per cent solution plus 5 per cent glucose, six showed increases of serum creatine with an associated creatinuria; two had increases in creatine in the urine and not in the blood; four had no change in the creatine of either the urine or the blood. Single creatine measurements were reported in thirty-nine patients not given injections; fifteen had creatinuria, often with a high serum level. These were usually in patients with severe symptoms; in several there was a fatal outcome.

Nitrogen Balance Studies. Most of the metabolic observations following the intravenous injection of amino acid mixtures have dealt with measurement of nitrogen balance. While one may question the value of such measurements as an indication of protein synthesis, it remains as our most single useful method of determining the ability of protein to be utilized by the body tissue. When carefully carried out with adequate controls, it is probably of considerable

value in determining whether an intravenous mixture of amino acids is actually utilized by the body for synthesis of tissue protein or whether it is simply deaminized and burned.

A provocative study of nitrogen balance was carried out by Cox et al.¹¹ in dogs in which various doses of different amino acid mixtures were given intravenously. It was found that at low levels of intake a mixture of crystalline amino acids maintained nitrogen balance better than in a similar level of amigen whereas at a high level of intake the reverse was true. The authors pointed out that the classification of an amino acid as essential is based upon the body's inability to synthesize it from other nitrogenous sources and that if only the essential amino acids are supplied the body must convert them to the so-called unessential amino acids. In this sense all the amino acids that go to form body protein are essential, and it is preferable for a protein hydrolysate to have both essential and unessential amino acids for maximum efficiency. One interesting finding was that although more amino acids were lost in the urine with the crystalline mixture than with amigen (including peptide losses), yet the nitrogen balance was similar in both cases. This, of course, raises the question as to how important certain peptides may be in promoting nitrogen utilization.

Comparative nitrogen balance studies have been made with different channels of administration. For example, Kade³⁵ measured the nitrogen balance in three dogs on a non-protein intake given parenterally intravenously and intraperitoneally and compared them with the oral intake of protein. The nitrogen balance was just as good with the intravenous as with the oral route. However, the intraperitoneal gave poorer nitrogen balance than the intravenous injections. Silber et al.⁵⁷ also found just as good nitrogen balance with an amino acid mixture given intravenously as orally even though there was a greater loss of amino acids in the urine during intravenous injections. The experiments were carried out

by first maintaining dogs on oral amino acids for forty days followed by twenty-four days of intravenous administration; the dose was 209 to 216 mg. of nitrogen per Kg. per day with the caloric intake 80 calories per Kg. per day. The amino acid mixture was apparently crystalline. In a similar experiment Sahyun⁵⁵ with a partially fortified acid casein hydrolysate found at an intake of 130 and 140 mg. of nitrogen per Kg. per day in one dog that the intravenous also gave just as good positive nitrogen balance as the period of oral intake which preceded and followed. However, in a second experiment the loss of nitrogen during the intravenous injection was greater.

Comparison of oral vs. intravenous administration was made in the human by Kozoll and Mok³⁸ who found that a lyophilized acid casein hydrolysate gave better nitrogen balance when given by mouth than when injected intravenously in seven of eight cases. Moreover, three of the eight gave positive balance with oral and negative balances with intravenous intake. Only one patient gave consistent positive balance but even here the oral was better in this respect than the intravenous period. These workers also found that a 1,000 calorie intake was optimum for nitrogen balance; increases did not improve utilization. A similar comparison with a different result was made by Bigham et al.³ who compared the intravenous utilization of an amino acid mixture with the oral utilization of protein. Three patients were given intravenous amigen for three days and then the same amount of nitrogen as protein by mouth; no significant difference was noted in any case. In the first patient nitrogen balance was +6 Gm. during the oral period, +1.5 during the intravenous; in the second patient -5.9 with oral, -6.4 with intravenous; in the third, +1.3 with oral and +1.5 with intravenous. Madden et al.⁴⁸ obtained similar positive nitrogen balances with amigen and a crystalline amino acid mixture given orally and intravenously in a patient with ulcerative colitis. However,

the patient obtained more clinical benefit from the period of parenteral administration.

Comparisons of nitrogen balance with various amino acid mixtures have been made by several observers. The effect of varying the period of hydrolysis was studied by Frost et al.²⁵ who injected partial acid hydrolysates of casein and of fibrin which had been digested for two, four, five and six hours. Although no detailed data were presented, no differences were reported in the utilization as shown by nitrogen balance; apparently the largest part of the utilizable protein material was broken down in two hours. The same workers²⁴ compared a partial acid hydrolysate of casein and of fibrin; negative balance, irrespective of the addition of dextrose, occurred with the casein hydrolysate when a level of 160 mg. of nitrogen per Kg. per day was used. A positive balance was possible with the fibrin hydrolysate at a much smaller dose of 110 mg. of nitrogen per Kg. per day. In a subsequent paper by the same authors²³ a similar difference was observed, i.e., a fibrin hydrolysate at a rate of 600 mg. of nitrogen per Kg. per day was retained better than a similar casein hydrolysate given at the same rate. This was also true with oral administration. Both hydrolysates contained 25 to 35 per cent of free amino acids. These results merely serve to emphasize that the hydrolytic method must be chosen to fit the protein employed since Christensen⁹ found that the acid hydrolysate of fibrin and the enzymic hydrolysate of casein gave identical nitrogen retentions in man.

The same partial acid hydrolysate of fibrin (aminosol) was used in humans by Koop et al.³⁶ When given at a rate of 0.52 Gm. of nitrogen and 33 calories per Kg. per day for four postoperative days after gastric resection, there was an average positive nitrogen balance of 16.3 Gm. This was compared with three patients subjected to gastric resection merely given intravenous glucose and the usual hospital diet in which there was a loss of 30, 46 and 56 Gm. of

nitrogen. The same author³⁷ carried out a much more extensive study of nitrogen balance in a series of surgical patients given parenamine, amigen, casein, aminosol, fibrin aminosol and gelatin. Of twelve patients given intravenous amino acid mixtures for five days after operation nine showed a negative balance varying between 0.1 to 8.9 Gm. per day whereas three showed a positive balance of 4.2, 5.0 and 8.0 Gm. The authors, however, subtracted 1 Gm. of nitrogen for fecal excretion even though no food was taken during this period.

Some metabolic data were described in a case described by Brunschwig et al.⁵ The patient had an extensive intestinal fistula and was maintained on an exclusively intravenous intake for eight weeks, during which time the wound healed remarkably and the patient was then operated upon without any difficulty. The daily intake was no greater than 980 calories, the nitrogen intake was only 6 Gm. daily as amigen. Yet during five days in which measurements were made the loss of nitrogen was but 0.78 Gm. per day. Doubtless had this intake of nitrogen been increased, the patient would have been in positive balance.

Nitrogen balance was studied with several other hydrolysates. White and Weinstein,⁷⁰ in a control series of patients who were given routine care after herniotomy, found an average loss of nitrogen during the seven postoperative days of 70.8 Gm. In one patient given intravenously 43.7 Gm. of nitrogen as "an enzymatic digest of mammalian protein" for seven days after cholecystectomy and appendectomy, the negative balance was only 19 Gm. In a second patient with intestinal obstruction who was given 53 Gm. of nitrogen there was a negative balance of 9.6 Gm.; the patient was in positive nitrogen balance for two days. Clinical observations showed excellent bedside recovery from operation including a sense of comfort and well being in the patients given the hydrolyzed protein as compared with the controls. Hoffman et al.,³¹ following the injection of a preparation of lyophilized casein hydrolysate with as-

partic and glutamic acid partially removed, observed positive nitrogen balance in nineteen of twenty patients given 42 to 340 mg. of nitrogen per Kg. per day as a 10 per cent solution.

The most extensive study on nitrogen balance with the vuj mixture of crystalline amino acids was carried out by Werner⁶⁸ who used an 8 per cent solution in seventy-three surgical patients, some for periods as long as three weeks. Some patients received 3 L. a day. In two healthy males the intravenous amino acid mixture was substituted for 60 of the 90 Gm. of protein in the diet with no change in nitrogen balance. In fifteen patients nitrogen balance was studied before operation. In some cases food also was given. As much as 32 to 37 Gm. of nitrogen per day were injected. In a few a comparison was made between the crystalline amino acids and amigen but no consistent difference was evident. One of the most striking findings was the fact that in one patient given both amigen and crystalline amino acids at the same time a daily positive nitrogen balance of as much as +16 to +20 Gm. was achieved. A consistent positive balance was not achieved in any of the other patients. In the postoperative patients (gastrectomies) nitrogen balance studies showed definite diminution in the degree of nitrogen loss in those given amino acids as compared with twenty-nine patients treated with the traditional routine. Moreover, the patients receiving amino acids left the hospital earlier; none had postoperative anastomotic obstruction as compared with five in the control group; temperatures returned to normal earlier; there was improvement in appetite and ability to eat; a sense of well being and restoration of strength was much greater than in the control group. Despite a caloric intake of only 1,000 or less, nitrogen balance was frequently achieved at a level of 15 Gm. of nitrogen intake.

Improvement in nitrogen balance by the addition of methionine to intravenous amigen was shown by Cox et al.¹² in dogs but not in man, presumably because man

has so little hair and thus needs less of the sulfur-containing amino acids.

PHYSIOLOGIC EFFECTS

Several observations have been made showing certain physiologic influences of the intravenous injection of amino acid mixtures. For example, Learner and his co-workers⁴¹ made extensive observations on dogs and humans following the intravenous injection of a 10 per cent amigen solution at a pH of 5. Gastrointestinal movements in the humans were measured through a Miller-Abbott tube previously passed. They found that the large contractions characteristic of normal duodenal movements disappeared during the injection. However, various tonus changes and an occasional large abnormal contraction were noted. These observations were correlated with the patient's subjective symptoms only in about one-half of the cases. Studies on the amino acid level of the blood showed an increase up to 6 to 11 mg. per cent. There was no change in the pH of the blood and the CO₂ combining power fell in only two cases from 63.4 to 59.6 volumes per cent. Crider and Walker,¹³ in a young female with a large fistula in her stomach, observed that the intravenous injection of an amino acid mixture had an inhibitory effect upon the resting activity as shown by a decrease in movement and in secretion. Lockhardt⁴³ found that the addition of an amino acid mixture to intravenous glucose apparently increased the utilization of glucose as shown by a reduction in the likelihood and degree of glycosuria.

CLINICAL OBSERVATIONS

Aside from the few patients experiencing untoward reactions most reports indicate a beneficial clinical effect following the use of intravenous amino acid mixtures. Many of these have been referred to previously. Davis¹⁵ compared the clinical effect of an intravenous protein hydrolysate (amigen) in 203 patients who received 730 L. during their postoperative period with fifty other

patients who received the usual injections of glucose and saline. Both groups were private patients operated upon for similar conditions by the author of the report. The latter group seemed weaker and slower in convalescence than those given the amino acid mixture. The reaction rate was 3 per cent, none severe. The author concluded that the addition of protein digest to the intravenous fluids was safe and efficacious in promoting general well being and strength, a quicker return of appetite and lessened fatigue.

Reifenstein⁵¹ studied a patient with a presumptive diagnosis of carcinoma of the stomach for twenty-four days, during which all of the intake was intravenous, including a solution of amigen. During this period the patient was always in positive nitrogen balance. This was not increased by increasing the glucose intake but was increased by adding additional amigen to the intravenous fluid. Clinical observations showed that hunger was not satisfied by the injection of glucose alone but was whenever amigen was added to the fluid.

Methods of Administration. Although most clinical reports deal with the intravenous injection of amino acid mixtures, several observations have indicated that the subcutaneous route is feasible. Crystalline amino acids in 8 per cent solution were so given twenty-five times in humans by Werner⁶⁸ and by Madden and his co-workers.⁴⁷ Hartmann²⁹ described a solution containing equal parts of 10 per cent amigen, 10 per cent glucose and lactate Ringer's solution which can be given satisfactorily by hypodermoclysis in babies. Madden et al.⁴⁵ noted that the subcutaneous injection of a crystalline amino acid mixture in dogs was utilized slightly better than the intravenous administration. Weinstein⁶⁷ gave 500 injections of hydrolyzed protein solution subcutaneously and 200 intravenously, apparently without difficulty, but no details were reported.

Value in Hepatic Disease. Although a high protein diet seems of established value in the therapy of hepatic disease, the intra-

venous use of amino acid mixtures has been considered dangerous by some, particularly in severe impairment in which a high amino acid level in the blood is known to occur. Indeed, several years ago Hopps and Campbell³³ described a fatality following the intravenous injection of amino acids in which autopsy showed severe hepatic damage. On the other hand, Stewart and Rourke⁶⁴ at about the same time found that patients with severe hepatitis tolerated intravenous injections of an amino acid mixture just as well as others. This was also the experience of Hecht³⁰ and of Emerson and Binkley.¹⁹ Lewis et al.⁴² studied this question specifically by injecting 45 Gm. of parenamine in 500 cc. intravenously during one hour in eight patients with Laennec's cirrhosis as compared with five normal controls. In general there was little difference in the plasma changes in urea or amino nitrogen of the two groups. In both groups there was the same incidence of nausea and vomiting.

That intravenous amino acid mixtures have a therapeutic value in hepatitis has been shown by two reports. Viswanathan⁶⁶ treated twenty-seven cases of infective hepatitis by the injection of 700 cc. a day for two, three or four days, the solutions containing 35 Gm. of papain hydrolysate of pork. As compared with an equal number of controls treated in the usual way, the injected patients recovered more rapidly. Most striking was the return of appetite which occurred in one-third to one-half the length of time noted in the controls. Simon and Brown⁵⁸ described a moribund patient with evidence of acute hepatic damage who recovered following the intravenous injection during four days of 3,500 cc. of a 5 per cent solution of a casein hydrolysate plus glucose. The kind of hydrolysate was not mentioned, but it produced marked phlebitis at the site of injection.

INDICATIONS FOR USE OF PARENTERAL AMINO ACID MIXTURES

It would seem unnecessary to prove that protein feeding is important, particularly

in surgical patients in whom there has already been much loss of protein tissue. Once this premise is accepted indications for the parenteral use of amino acid mixtures depend upon the answer to two questions: First, is the mixture utilized as protein nourishment when given as a parenteral injection? Second, is this method of administration indicated? The first question obviously depends upon the kind of amino acid mixture used. Sufficient evidence has been obtained to show that many of the preparations now available are actually utilized as protein nourishment. Much of this evidence has been summarized previously.¹⁸ The present review contains additional data. The second question is answered by considering the particular patient about whom the decision must be made. The answer is obvious in the case of individuals unable to take any nourishment by mouth and they include all patients given injections of water and glucose for purposes of nutrition. In all such patients it seems clear that appropriate amino acid mixtures should be added in order to prevent further protein starvation. If we accept the need for protein food by mouth, then we must use the same criterion in patients unable to eat.

Parenteral amino acid mixtures are also indicated in patients who are able to eat but in whom better clinical results will be obtained if the patient's gastrointestinal tract is kept completely at rest. These include patients with various infections such as peritonitis, regional ileitis, certain peptic ulcers and particularly patients with intestinal fistulas from which most if not all of the nourishment is being lost before adequate absorption. Complete rest of the gastrointestinal tract is also of especial value in many patients being prepared for operation because such preparation permits complete evacuation of the gastrointestinal tract. Intravenous feeding during this period leads to adequate nutrition of the tissues and, with the aid of blood and plasma transfusions, correction of edema. In this way operations upon the gastrointestinal tract are made easier technically and heal-

ing is more certain after operation. The value of adding an amino acid mixture to parenteral injections in the treatment of ulcerative colitis has been suggested in the single case reports already mentioned, e.g., Remington et al.⁵² and Madden et al.⁴⁸ More striking has been the experience of Paulson⁵⁰ who treated fourteen serious cases of ulcerative colitis with total intravenous alimentation, using an amino acid mixture (amigen) and dextrose, with pronounced clinical benefit.

Clinical benefit may be obtained in patients able to digest food, although in limited amounts, from parenteral amino acid mixtures. This represents a supplementary method of administering protein nourishment; it may serve to accelerate the return to normal and thus shorten the period of nutritional rehabilitation in extremely malnourished patients. It is also probable that in extreme starvation the parenteral route may be the only method available to rescue patients from the otherwise irreversible stage which is occasionally seen when there is total inability to absorb even liquids by mouth.

Dose of Amino Acids. The amount of amino acid mixture required for parenteral injection has not been clearly established. As much as 30 or more Gm. of nitrogen have been injected per day; this represents the equivalent of over 180 Gm. of protein. Ordinarily the author has used as routine a daily intake of 100 Gm. each of amino acid mixture and 100 Gm. of glucose in 2,000 cc. of solution containing about 5 Gm. of sodium chloride. This is given in two 1 L. injections as 5 per cent amigen, 5 per cent glucose, one in the morning, one in the afternoon or evening. Each injection usually requires about two hours. Parenteral vitamins may be injected at the same time or given separately. The caloric requirements are, of course, inadequately met by such a parenteral diet. Previously reported evidence has shown that the rest of the energy needs may readily and safely be met by adipose tissue.¹⁸ Further evidence has confirmed this basic concept.^{38,68} Moreover,

Gamble²⁶ has found no increase in protein sparing effect when the glucose intake in humans was increased from 100 to 200 Gm. Cannon⁷ could reduce the caloric intake of rats to 70 per cent of normal without influencing nitrogen balance. Thus it would seem that for short periods of time at least the glucose intake can be safely limited to 100 Gm. That a less than full caloric parenteral intake of glucose will not lead to ketosis was illustrated in a case described by Brunshwig et al.⁶ The patient was fed exclusively by vein for eight days with 2 L. of amigen a day plus blood and glucose and gelatin following removal of all of the pancreas and duodenum, stomach and spleen. The urine output was over 1,400 cc. a day. Although the total daily glucose intake did not exceed 200 Gm., usually 150 Gm., no acetone or acetic acid was found in the urine at any time.

An intake of 100 Gm. each of an amino acid mixture and glucose in an average-sized adult probably will not lead to the deposition of much tissue protein; however, it will minimize or eliminate entirely the metabolic loss of tissue protein in most cases in which it is indicated. The reports indicating its clinical benefit are numerous but have not been reviewed herein because of the absence of objective data. It seems clear, however, that most if not all of the advantages of protein feeding by mouth can be readily achieved in patients unable to eat by this form of protein alimentation. The parenteral route, however, must always be viewed as a temporary expedient aimed at restoring the patient as rapidly as possible so that he may take all of his nutritional needs by mouth. Full tissue repletion can probably be achieved only through the normal channel.

It should be emphasized that amino acid mixtures serve merely as building blocks for protein synthesis for the body and that other forms of parenteral protein, i.e., hemoglobin as red cells and plasma proteins are nearly always indicated in protein-depleted patients. This is particularly true of loss of red cells which can be readily and

permanently replaced. Injections of plasma and particularly salt-poor albumin are also useful in protein-deficient patients even though they have many disadvantages when used as the sole source of protein intake. In the complete care of protein-depleted patients requiring parenteral therapy one should employ each of the three forms of protein administration, i.e., hemoglobin as red cells, plasma albumin as such or as plasma and amino acid mixtures.

SUMMARY

Review of the literature since 1945 has confirmed previous studies regarding the safety and utility of appropriate amino acid mixtures as parenteral protein food. The addition of such solutions to the parenteral fluids given for purposes of maintenance assures an almost complete nutritional intake during periods when the patient is unable to take anything by mouth and/or when we wish to keep the gastrointestinal tract completely at rest. Supplementary protein alimentation may also be useful by this method. Use of parenteral amino acid mixtures enables the physician to treat disease without protein starvation. Since protein starvation is known to be detrimental, the boundaries of surgical or medical therapy, previously limited thereby, can now be greatly extended.

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Case Reports

Spontaneous Rupture of the Heart Due to Myocardial Infarction*

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RUPTURE of the heart subsequent to myocardial infarction is a lesion which, while well understood, is but seldom appreciated. Its occurrence is dramatic and its presence ominous.

Krumbhaar and Crowell⁴ reported 654 cases of spontaneous rupture of the heart due to myocardial infarction; these include twenty-two of their own and 632 collected from the literature. Seven instances were seen at the Philadelphia General Hospital among 16,000 autopsies. Friedman and White² quote Martland as "finding rupture of the myocardium as a cause of death in 42 (2.1 per cent) of 2,000 cases of individuals who died suddenly; all of the 2,000 cases were over 10 years old, the majority being between 40 and 65, five-sixths males and one-sixth females." Friedman and White state further, "Among 25,000 post-mortem examinations at the Los Angeles County Hospital from 1924 to 1941 there were 865 cases of unhealed myocardial infarction, of which 72 (8 per cent) showed cardiac rupture."¹ (Table I.)

At the Massachusetts General Hospital Friedman and White examined the protocols of 2967 autopsies, in 270 of which myocardial infarction was observed; acute infarction in 105 of the 270, and old coronary occlusion with healed infarction in 165. "In this latter group numerous ventricular aneurysms were found but not a single case of rupture occurred. Of the 105 cases of acute infarction, all occurring within two weeks of death, 10 had as the immediate cause of death a rupture of the ventricle with tamponade from hemopericardium."

As opposed to a 3.7 per cent rate of rupture following acute myocardial infarction in general hospital patients, Jetter and White³ found that sixteen of twenty-two (73 per cent) mentally ill patients with acute myocardial infarction developed the

TABLE I
SPONTANEOUS RUPTURE OF THE HEART
DUE TO MYOCARDIAL INFARCTION

Author	No. Autopsies	Cases of Myocardial Infarction	Cases of Cardiac Rupture	Per Cent of Cases of Infarction Showing Rupture
Krumbhaar and Crowell	47,000	...	23	
Martland.....	2,000	304	42	13.8
Edmondson and Hoxie.....	25,000	865	72	8.0
Friedman and White.....	2,967	270	10	3.7

sequence of cardiac rupture: hemopericardium, cardiac tamponade and death.

The mean age of patients dying from cardiac rupture is 65.7 years and in mentally ill persons with the same lesion 66.5 years. This complication is apt to occur between the tenth to fourteenth day from initial onset of symptoms of myocardial infarction.

CASE REPORT

A forty-two year old white male was admitted to the Madigan General Hospital on October 22, 1946, with chief complaints of nausea and malaise. The family history contributed little except that one sister had died of pulmonary tuberculosis. Beyond the usual childhood diseases

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the patient's own past history was unremarkable except that in August, 1944, he was diagnosed as having an active duodenal ulcer and was treated for the same complaints in June, 1946.

In October, 1946, the patient went on a hunting trip and in the field complained of easy fatigability and extreme weakness. He hiked extensively for two days and experienced no dyspnea, chest pain or other striking symptoms. After returning home on October 21, 1946, he felt marked malaise, became quite nauseated and then vomited several times. This was at 8:00 P.M. At 10:30 P.M. he felt severe constriction over the precordium and beneath the upper and middle thirds of the sternum. This discomfort he described as "tightness" and a feeling as though "hands were pulling together in my chest." Intermittent pain occurred every thirty minutes during the night but by 8:00 A.M. the pain disappeared. Two hours later on October 22, 1946, the symptoms reappeared and were aggravated every fifteen minutes. Their location was similar to the previous distress but for the first time there was radiation from the anterior axillary regions down both arms on the medial aspects to the wrists. By 1:00 P.M. the pain continued so intense that a physician was called. After 15.0 mg. of morphine sulfate were given by hypodermic injection there was some relief. Within the first thirty hours the patient had vomited ten or twelve times. He was hospitalized on October 22, 1946.

Dyspnea became evident after admission and the patient broke out into a cold sweat and became obviously pallid. On admission physical examination revealed some slight tenderness on deep palpation in both upper quadrants and in the epigastrium. The pulse rate was 96 per minute; respiratory rate 24 per minute and the temperature 97.6°F. orally; blood pressure reading was 130/80 mm. Hg; no other pertinent cardiac findings were noted.

Laboratory studies on October 22nd showed: white blood count, 9,500; neutrophils, 80 per cent; lymphocytes, 16 per cent; monocytes, 2 per cent; eosinophiles, 2 per cent. On October 24th the white blood count was 20,100; neutrophils, 82 per cent; lymphocytes, 10 per cent; monocytes, 8 per cent.

Serologic tests were negative as was a urinalysis on admission. The sedimentation rate on October 22nd was 31 mm. per hour (Wintrobe method). An x-ray film of the heart and lungs showed a picture compatible with the presence

of early pulmonary edema. Electrocardiograms were taken and are shown in Figure 1.

On October 23, 1946, the temperature climbed to 102°F. No new systems developed but physical examination showed a respiratory rate of 26 per minute, pulse rate of 128 per minute and a blood pressure of 90/70 mm. Hg. The heart sounds were distant and gallop rhythm appeared. No friction rub could be heard and no major changes occurred until November 1st when the patient complained of abdominal distention. Symptomatic therapy failed to relieve this complaint.

Twelve days after admission the patient was being examined routinely. At that time he was perfectly alert and in a cheerful mood although he complained of considerable substernal pain without radiation in the upper and middle regions which was aggravated by moderately deep respiratory efforts. His respiratory rate was 24 per minute and pulse 140 per minute; the blood pressure was not yet taken. A few premature ventricular contractions were heard. Suddenly and without warning the patient tensed all his muscles, straightened out rigidly, the neck dropped backward in opisthotonic fashion and tonic and clonic convulsions shook him for a few seconds. Following a slight groan, his eyes became fixed in lateral strabismus and vivid cyanosis developed instantaneously. During this time one of us (F. C. M.) was auscultating the heart. No friction rub was heard before this spectacular episode but immediately after its inception an intense, grating pericardial rub was audible from the third left interspace down to the apex. Unfortunately, we had taken the stethoscope off the chest for a moment prior to the appearance of the pericardial rub to answer a question; so if rupture of the ventricle occurred at this instant, we did not actually hear it. Within three minutes after the onset of the episode the patient was dead, respiratory efforts ceasing but several seconds before cardiac action no longer was detectable.

The postmortem examination revealed the following: The subject was moderately obese, measuring 66 inches in height and weighing 180 pounds. Peripheral edema was absent. The heart was completely surrounded by 200 Gm. of recently clotted blood when the pericardium was opened. Petechial hemorrhages were noted on the exterior of the pericardial sac, with ecchymoses in the adjacent left mediastinal fat. The epicardium and parietal peri-

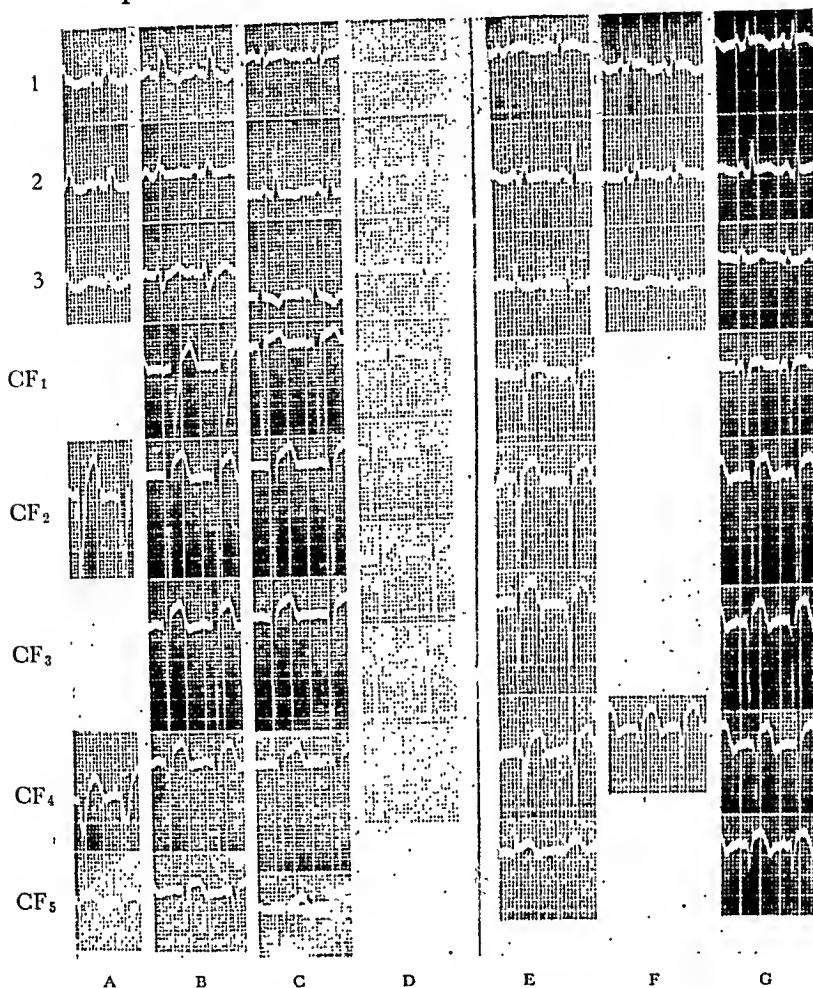


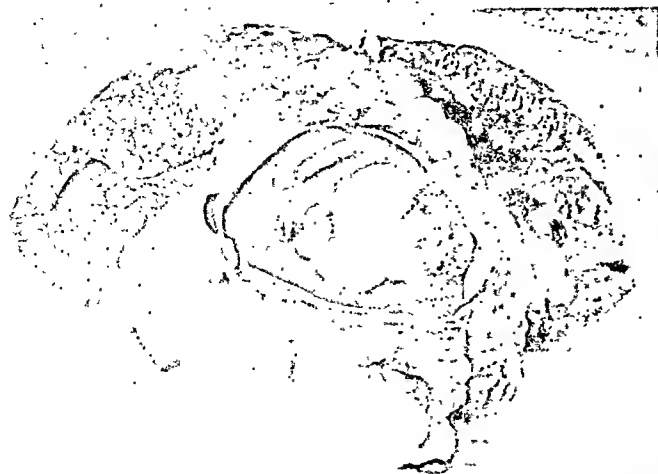
FIG. 1. A, tracing taken October 23, 1946. QRS₁ widened with slurring of R wave. T₁ inverted. Downward bowing of ST segment in leads 1 and 2. R wave absent in lead CF₄. B, tracing taken October 24th. T₁ inverted. R waves absent in precordial leads. C, tracing taken October 25th. T₂ and T₃ inverted. D, tracing taken October 28th. T₁ almost isoelectric. T₂ flattened; convex bowing of S-T segment in lead CF₅. E, tracing taken October 29th; minimal elevation of S-T segment in lead 2. T₃ diphasic. S-T segment elevated in lead CF₅. F, tracing taken November 1st. S-T segment elevated over 1.0 mm. in Lead 1, with coving of T₁. S-T segment elevated in Lead 2; note beginning inversion of T in CF₄. G, tracing taken November 1st. Elevation of ST₁ and ST₂ apparent, with sharper inversion of T₁. Note the ST-T pattern in leads CF₃, CF₄ and CF₅.

cardium over the entire left ventricle showed fine fibrinous roughening without adhesions.

The heart weighed 450 Gm. Subpericardial fat appeared excessive, exteriorly, and on the anterior surface of the apex there was a jagged, vertical tear parallel to and immediately to the left of the interventricular septum. The defect was 2.5 cm. in length. The torn edges of the left ventricular wall (here thinned to 2 mm. thickness over an area 2 cm. in diameter) gaped slightly, revealing a partially protruding, spherical, mural thrombus. This was 2 cm. in diameter and firmly attached adjacent to the aperture.

Interiorly the left ventricular endocardium showed extensive mural thrombi in sheet-like attachment anteriorly and medially over an area 3 by 1.5 cm. The sectioned myocardium showed an irregularly outlined, yellow-gray area of slight softening involving the left anterior quadrant of the interventricular septum and extending anteriorly, laterally and inferiorly to include all except the posterior wall of the left ventricle.

All main coronary arteries showed tortuosity and moderate deposition of atheromatous plaques without ulceration or calcification.



2



3

FIG. 2. Gross specimen showing heart lying within pericardial sac. Darkest areas are blood, surrounding heart (hemo-pericardium). The necrotic, friable apex is visible, with a lesser circular area of infarction surrounding it.

FIG. 3. Gross specimen showing site of ventricular rupture (apex of left ventricle) surrounded by area of necrosis. Extension of the rupture line was made at autopsy.

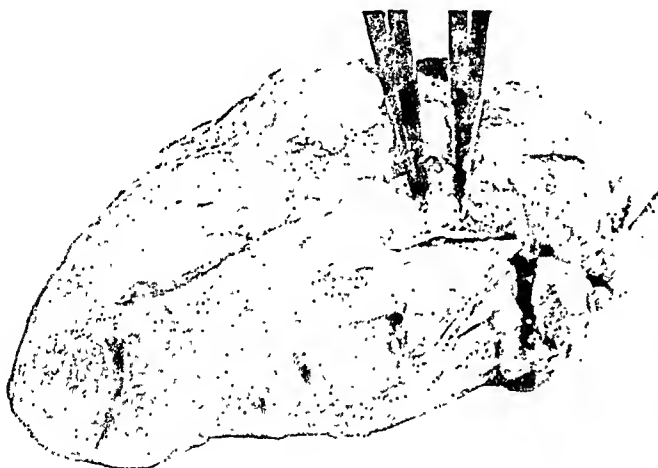


FIG. 4. Left lateral view of heart, again showing the site of rupture at the cardiac apex. Narrowing of the coronary artery is seen in its upper one-third with evidence of ulceration and plaque formation.



FIG. 5. The heart, in gross, with left ventricle exposed to show the aneurysmal thinning of the myocardium over the area of infarction and the friable, necrotic tissue overlying a large intramural clot.

Patency was maintained throughout except for a distance of 1 cm. along the anterior descending branch of the left coronary artery at a point 1.5 cm. from the latter's ostium. Here a subintimal purplish bleb had narrowed the lumen to pinhead size. Immediately distal a 2 mm. partially occluding thrombus was seen. (Figs. 2 to 5.)

Recent infarction involved the upper one-third of the spleen and a portion of the right kidney. Gallbladder, stomach and duodenum

were without gross abnormality and generalized arteriosclerosis was slight.

Microscopically the infarction of the myocardium revealed extreme variations in the microscopic picture; areas of finely collagenous but highly cellular fibrous tissue with proliferating fibroblasts alternated with "sequesters" of completely necrotic muscle, as yet uninvaded by exudate and surrounded by pigmented macrophages and fibroblasts. In a few places polymorphonuclear activity among necrotic muscle

fibers was still apparent, chiefly about the area of rupture. At the site of rupture the thinned wall consisted largely of an unabsorbed sub-endocardial "sequestrum" of necrotic muscle without interior reactions, bounded peripherally by a thin zone of granulation tissue into which widespread interstitial hemorrhage had occurred. Most peripheral lay a thin layer of sub-epicardial muscle fibers showing intense polymorphonuclear infiltration. (Fig. 6.)

The anterior descending coronary artery showed a fairly recent subintimal hemorrhage in an atheromatous area surrounded by extreme intimal fibrosis and medial atrophy. Calcification was absent. The partially occluding, adjacent mural thrombus was found to be incompletely organized.

COMMENT

The degree of fibrosis present in some areas suggests healing of more than two weeks' duration, but the cellular activity of the lesion as well as the fact that previous studies⁵ have shown collagen deposition to begin, on the average, at about the twelfth day make the postulation of another, earlier episode of infarction here insecure. Ruptures have been found to occur more often in initial infarctions than in succeeding episodes¹ and more often within the first week following the occlusion than in the second week.⁵ The numerous areas of unabsorbed necrotic muscle persisting in this massive infarct seem to offer the best explanation for the belated rupture. Such

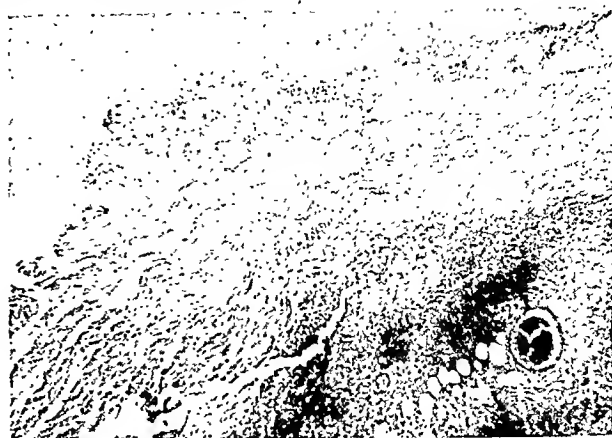


FIG. 6. Photomicrograph of left ventricular wall with site of rupture at extreme left, showing mass of necrotic fibers. Pericardium (top) shows inflammatory thickening. Centrally, and lower right interstitial hemorrhage is seen.

areas not uncommonly remain for weeks but are usually less extensive.

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Bundle Branch Block with Spontaneous Remission While Taking an Electrocardiogram

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THIS case is reported because a careful search of the literature has failed to reveal any case in which

CASE REPORT

J. B., aged forty-two, reported for a heart examination October 29, 1945. His history was

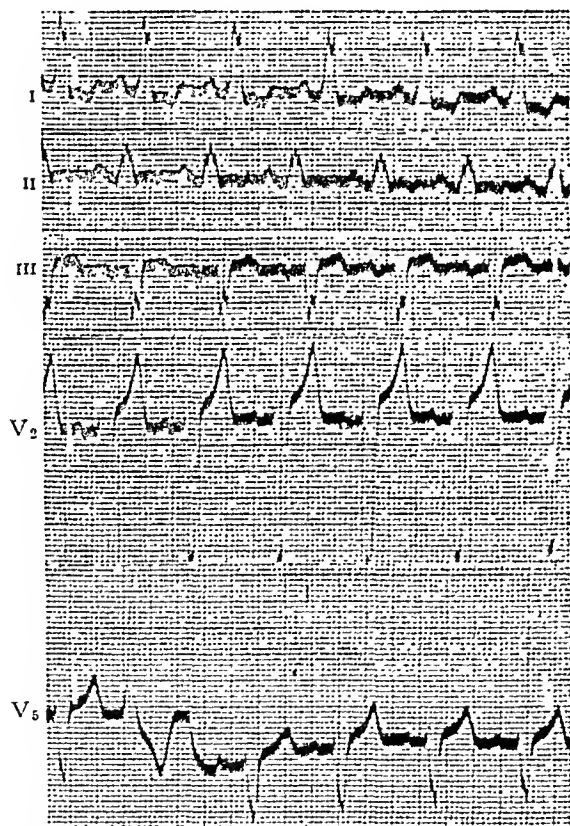


FIG. 1. Regular sinus rhythm. Rate 88, PR, 0.20, QRS, 0.12. Left axis deviation; one premature beat in lead V_5 . Left bundle branch block of the discordant type. Left ventricular strain pattern. The three top leads are limb leads I, II and III. The precordial leads are designated as V_2 and V_5 .

bundle branch block disappeared spontaneously while having an electrocardiographic record made.

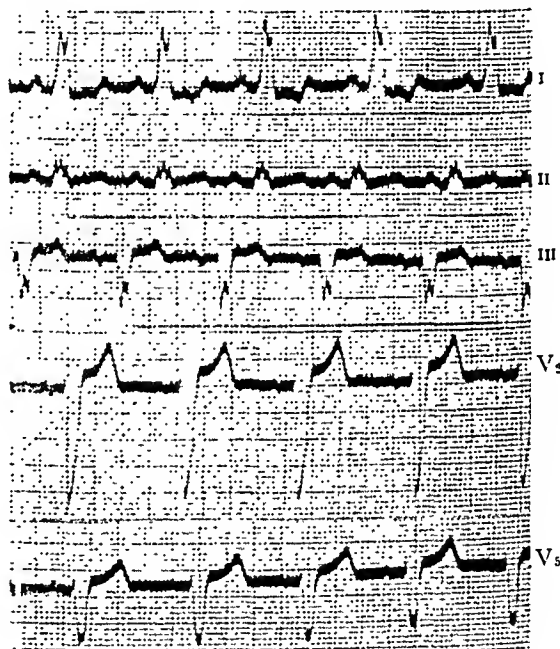


FIG. 2. Standardization 3 cm.-3. ml. Precordial leads are designated as V_2 and V_5 . The only change of note is a slight decrease in the potential of the T waves in the precordial leads.

not typical of an acute coronary occlusion, but he stated that for the past two months he had been treated for low blood pressure and anemia.

He was a tall, well developed white male. His height was 6 feet 2 inches; weight, 279 pounds; vital capacity, 5,500 cc., 111 per cent; red blood cells, 4,200,000; white blood cells, 6600; hemoglobin, 12 Gm.; polymorphonuclears, 72 per cent; lymphocytes, 26 per cent; juveniles, —2 per cent. His heart was definitely enlarged on percussion. The sounds were clear and dis-

ting. A faint suggestive systolic murmur was heard over the apex and many premature beats were noted.

An ECG taken October 29, 1945, (Fig. 1) showed a typical picture of left bundle branch block of the discordant type. There was a left ventricular strain pattern with a prolonged PR and QRS interval. One ventricular premature beat was noted in precordial lead V₅. The precordial leads were taken with the unipolar lead from a central terminal.

Another ECG was taken on December 7, 1945. (Fig. 2.) This picture is essentially the same as the previous one. There is a change in the potential of the T waves in the precordial leads.

Another ECG was taken on April 15, 1946. (Fig. 3.) This picture shows the first two beats in lead I to be the typical QRS complex of bundle branch block. From the third beat on the QRS complex has changed suddenly to a fairly normal appearance. The QRS complexes have lost their bundle branch appearance and look normal. There is a definite Q₁. The QRS complexes are all of high potential. ST₁ is flattened and depressed and T₁ is diphasic. T₂ and T₃ are now erect. A recent ECG has shown no change from this picture.

DISCUSSION

Transient complete bundle branch block has been rather infrequently reported. Kurtz,¹ Master, Dack and Jaffe² have reported cases of transient bundle branch block which later became permanent. Kalett³ reported a case of bundle branch block with spontaneous remission after four years.

CONCLUSION

I have reported a case of bundle branch block which to my personal knowledge lasted seven months and which spontaneously returned to normal while having an ECG record made.

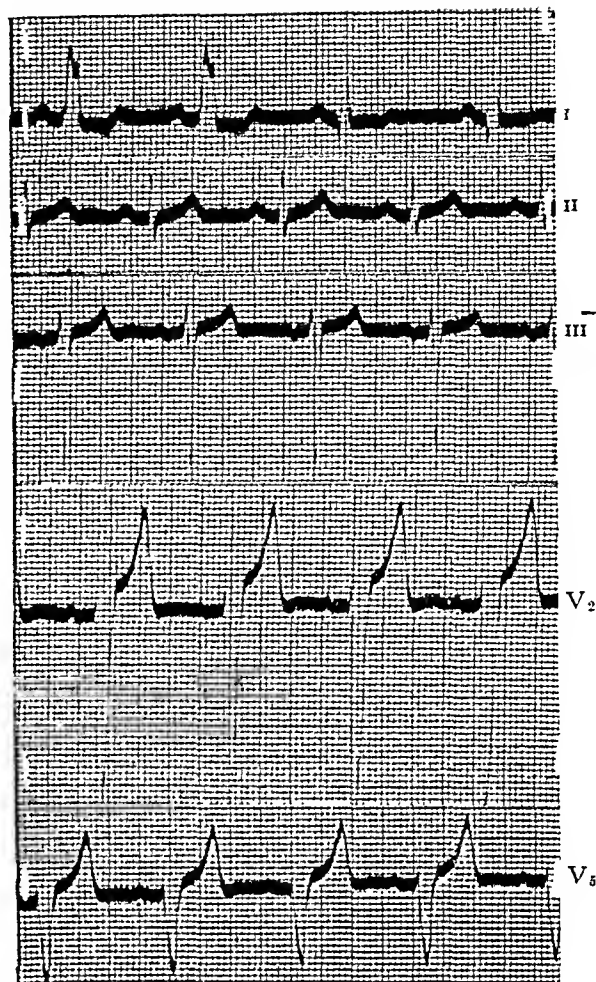


FIG. 3. Standardization 3 cm.-3 ml. Precordial leads designated by V₂ and V₅. The first two QRS complexes in lead I are the typical bundle branch block picture. The QRS complexes III and IV show a return to a normal appearance; this appearance continues on through the balance of the tracing. The remainder of the picture is the typical pattern of left ventricular strain.

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Book Review

Cornell Conferences on Therapy. Volume Three. Harry Gold, M.D., managing editor. Vol. 3, pp. 337. New York, 1948. The Macmillan Co.

This is the third of the well known series of Cornell University Medical College Conferences on Therapy, stenographic reports of discussions conducted by members of the Departments of Pharmacology and of Medicine, with the collaboration of members of other departments and institutions. The fifteen conferences included have been carefully selected and edited with the view of ensuring timeliness and general interest. This is apparent from the choice of conferences which include a basic discussion of the dose of a drug; lively exchanges of opinion concerning the management of congestive failure, uses of protein hydrolysates (with a special conference on relation to management of peptic ulcer), treatment of alcoholism, management of pain due to muscle spasm, the rational use of cathartic agents and informative discussions of the uses of streptomycin, of BAL and of the treatment of pneumonia, hepatic insufficiency, thrombophlebitis, infections of the genito-urinary tract and barbiturate poisoning.

The Cornell Conferences on Therapy are designed "to stimulate interest in rational therapy" by integrating the points of view

of the disciplined pharmacologist and the experienced clinician. Each conference is introduced with an authoritative discussion of the basic principles of the subject under consideration which is then followed by "spontaneous, informal and free discussion" reflecting different shades of opinion and experience. The result is a series of informed and well integrated clinics of sustained interest, with answers to many questions that crop up continually in the practice of medicine but somehow rarely appear in textbooks and other formal presentations.

Volume 3 of this series sustains the high standards of its predecessors; indeed, some of the conferences included are, if anything, even more sophisticated and designingly wrought. They may be read and re-read with profit and pleasure. To the practicing physician they bring a critical evaluation of newer therapeutic agents and an unprejudiced re-evaluation of some of the old. The medical student and young physician preparing for his Board examinations will appreciate these exercises taken directly from the classrooms of one of our great medical schools. As teaching texts and material for discussion in small groups and journal clubs the reviewer has found the conferences invaluable.

A.B.G.

Editorial

The American Journal of Medicine Seminars on Hypertension

IN the first six issues of the current year The American Journal of Medicine was the forum for a series of seminars covering the field of experimental and human hypertension. These articles presented the seasoned opinions of a group of investigators with wide experience in one or another aspect of this problem. As was to be expected in a field of study which has not advanced to a point at which conclusive answers to crucial questions can be given, important differences in viewpoints were disclosed, not only with respect to the mechanisms responsible for the development of experimental renal and essential hypertension but also as to the relationship between the two conditions. That these controversial aspects could now be so clearly formulated as to provide specific challenges to be met by appropriate experimentation is in itself a sign of healthy progress. Any undue pessimism about the present state of the hypertension problem or its future development would seem unwarranted in the light of the extraordinary advances of the decade and a half since the classical experiments of Goldblatt ushered in the modern era in the study of hypertension.

What stands out as particularly characteristic of this period is the significant advance in experimental technics. The development by Goldblatt of a method by which hypertension could be produced regularly in animals provided the tool which made it possible to gain many new and

important insights into the mechanisms by which hypertension might arise. More comprehensive and exact procedures for studying hemodynamics in animals and man furnished additional criteria for evaluating the relationship between essential hypertension and a variety of experimental hypertensive states in animals. The introduction, particularly by Smith and his associates, of more specific measures for estimating renal excretory function and blood flow has proved of special value in view of the central position which the kidney has tended to assume in this problem. In addition to these newer tools there has grown up a new way of thinking which utilizes a multi-disciplined approach in seeking to relate hypertension to underlying metabolic and endocrine processes.

Perhaps the outstanding result of the systematic exploration of experimental renal hypertension produced by the Goldblatt clamp or the perinephritic technic of Page was the accumulation of evidence that a humoral mechanism, primarily of renal origin, may play an important rôle in this syndrome. The elucidation of this mechanism, which began with the original experiments on renin by Tigerstedt and Bergmann in 1898, is a brilliant chapter in the history of hypertension. Only the barest outlines need be sketched here. The basic principle of this humoral mechanism is the kidney enzyme, renin. Undetectable in the blood under normal circumstances, applica-

tion of the Goldblatt clamp leads to its prompt appearance in measurable amounts in the renal vein, and later in the systemic blood. Itself devoid of vasoconstrictor activity, it acts upon a pseudoglobulin substrate in plasma, termed hypertensinogen, to form the pressor principle, hypertensin (angiotonin), which is subsequently destroyed by an enzyme, hypertensinase, present in many tissues, including red blood cells. The analysis of the steps in this humoral mechanism is due in large measure to the efforts of many investigators in this country and South America, the work of Braun-Menendez and co-workers and of Page and his associates in identifying the pressor activity with hypertensin rather than renin representing a major contribution.

It is probable that this description of the renin-humoral system will prove to be essentially correct at least in its broader outlines; when the important components of the system have been isolated in pure form, it may require modification in certain details. The description is, however, still incomplete in at least one very important respect; there is no certain knowledge as to the nature of the stimulus which leads to the release of renin from the kidney. Of the two divergent viewpoints the more generally held is that renin discharge can best be related to renal ischemia. There is strong supportive evidence for the existence of renal ischemia immediately after application of the Goldblatt clamp, but it is still not established that a permanent reduction of renal blood flow is necessary for the persistence of hypertension in animals. Page and Corcoran, on the basis of renal blood flow and clearance studies, reject the ischemia concept and postulate that the release of renin is the result of an alteration in renal hemodynamics, most likely a reduction in intrarenal pulse pressure. However, the evidence offered by Page and his co-workers for renin release by kidneys perfused at low pulse pressures under aerobic conditions has been subjected to criticism on methodologic grounds.

The nature of the stimulus for renin dis-

charge is not just of academic interest. The analysis of the mechanisms regulating renin metabolism within the kidney may well prove to be of primary importance for elucidation of the relation between experimental renal and essential hypertension. Except for the regular occurrence of renin in the kidney and its discharge following acute renal ischemia, there is virtually no knowledge of the factors which may condition its participation in the vascular economy of the organism. Does the renin mechanism take part in circulatory homeostasis under normal conditions or is it an emergency mechanism operative only in states of stress? Does it assist in regulating intrarenal hemodynamics under normotensive conditions by attaining local concentrations sufficient to induce renal arteriolar constriction but too low for peripheral pressor effects? What is the nature of the mechanisms by which renin is apparently retained within the kidney cell under certain conditions (e.g., aerobiosis) and released under others (e.g., anaerobiosis)? Does the kidney also possess a mechanism for inactivating renin? This possibility is suggested by the observation that when only one kidney is clamped and the other left intact, the resultant hypertension is transitory, presumably because of the protective action of the hypertrophied unclamped kidney. If such an inactivating mechanism exists, is it subject to deterioration under conditions other than anoxia and would its deterioration lead to an unrestrained release of renin even under aerobic conditions? These and other related questions urgently need answering. In the meantime we can scrutinize the present evidence for a causative rôle of this renal-humoral mechanism in experimental renal hypertension.

Two types of evidence are favorable to such a rôle. During the rise of blood pressure following partial constriction of the renal arteries renin appears in measurable and increasing amounts in the systemic circulation. Second, the intravenous injection of hypertensin in animals and man reproduces with reasonable fidelity the hemodynamic

picture characteristic of experimental renal and essential hypertension. Thus, hypertensin *could* produce the type of hypertension with which we are concerned, and abnormal amounts of its progenitor, renin, *are* present in the blood during the acute stage of experimental renal hypertension.

However, during the chronic stage of this syndrome, despite a persistent elevation of blood pressure, the renin content of the blood gradually falls until renin is no longer detectable by any of the present methods of assay. Several interpretations of this phenomenon have been advanced. The renin mechanism may play no significant rôle in the development of renal hypertension, the increased humoral content being coincidental rather than causal. Or the action of renin may be limited to initiation of the hypertensive syndrome which is subsequently maintained by other pressor agents or by a neurogenic mechanism mediated through the sympathetic nervous system as suggested by Ogden. An alternative hypothesis has been advanced by Grollman and his associates that the chronic stage of hypertension is due to the *lack* of some kidney principle which is essential for the maintenance of normal blood pressure. Finally, the possibility has been recognized that the absence of renin is only apparent and due to the lack of sensitivity of the current methods for its assay; thus, although the renin content of the blood during the chronic stage falls well below the measurable amounts characteristic of the acute stage of hypertension, the concentration may still be sufficiently great to maintain hypertension, particularly in an organism which in some manner may have become sensitized to its action.

At this juncture the renin theory received support of another character from the observations of Wakerlin and his associates that the repeated injection of heterologous renin extracts of kidney led to the development of antirenin activity in blood, caused a fall to normal of the blood pressure of dogs with renal hypertension and prevented the development of hypertension

following constriction of the renal arteries. More recently Wakerlin has expressed some uncertainty because of discrepancies between antirenin titers in blood and the degree of protection observed, whether to attribute the modification of the hypertensive syndrome to antirenin or to immune bodies related to other as yet unknown principles in the renal extracts he employed as antigens. Goldblatt, however, does not consider conclusive the evidence upon which Wakerlin questions the significance of antirenin.

These uncertainties in regard to the rôle of renin, particularly in the chronic stage, have stimulated the search for other pressor agents which might be implicated in the development of renal hypertension. Suspicion first fell on the pressor amines, such as tyramine and hydroxytyramine, and was strengthened by the observation by Holtz that kidney pulp converted tyrosine into tyramine, particularly under anaerobic conditions, and by Bing that the totally ischemic kidney transformed dopa (*l*-di-hydroxy-phenylalanine) into a pressor substance with some of the properties of hydroxytyramine. On the basis of these findings Schroeder injected tyrosinase intravenously into hypertensive dogs, rats and humans and observed a reduction in blood pressure which did not occur in normal controls. Despite this suggestive evidence, Page, in a review of the subject, concludes that there are many serious objections to the amine intoxication theory which militate against its playing an important rôle, at least in the early course of the disease; he lays particular stress on the significant differences between the hemodynamic phenomena of the pressor amines and those characteristic of experimental renal and essential hypertension.

Shipley, Helmer and Kohlstaedt recently described a pressor principle present in renal extracts and in the blood of cats dying of various causes or in hemorrhagic hypotension. Intravenous injection of such blood or renal extracts results in a sustained elevation of blood pressure in test animals

bilaterally nephrectomized thirty-six to forty-eight hours previously but not in normal controls. This principle appears to be protein in nature and distinct from renin and hypertensin as well as from the pressor amines. It has not as yet been found in the blood in hypertension. In view of its sustained pressor effect further study of this principle will be watched with great interest.

Another set of recently described vasotropic principles also distinct from renin and hypertensin has been found to be involved in the syndrome of experimental renal hypertension (Shorr, Zweifach, Furehgott, Mazur and Bacz). These consist of a renal vasoexcitor, termed VEM, and a hepatic vasodepressor, VDM, with opposite actions on the muscular vessels of the terminal vascular bed just distal to the arterioles upon which hypertensin acts. VEM enhances the vasomotion and constrictor activity of the terminal arterioles and precapillary sphincters and increases their reactivity to topically applied epinephrine; VDM induces opposite effects on the same vessels. Their opposing actions on the terminal vascular bed are such as to suggest that they constitute a homeostatic system for the regulation of the peripheral circulation. VDM and VEM arise in liver and kidney, respectively, under anaerobic conditions; they are inactivated under aerobic conditions by the organs in which they are formed; these reactions are presumed to be of enzymatic nature.

These principles develop in experimental renal hypertension in the following manner: Within a few minutes of the application of the Goldblatt clamp, VEM, normally undetectable in blood by current assay methods, appears in renal vein blood and shortly thereafter in the systemic circulation. Its appearance has been traced to a deterioration following constriction of the renal arteries of the renal mechanism by which VEM formation is inhibited under aerobic conditions; as a result VEM is produced continuously under both aerobic and anaerobic conditions. VEM continues

to be present in the blood throughout the period of rising blood pressure; however, when the chronic stage has set in, VEM usually is no longer detectable, a situation which at first appeared to be analogous to the disappearance of renin during the chronic stage. However, this "neutral" state of the blood was found to be due not to the disappearance of VEM (which by appropriate methods could be shown to persist in high concentrations) but to the appearance of equally high concentrations of VDM released by the liver. The nature and locus of action of VEM suggest that its potential effect upon peripheral resistance and blood pressure would be of an indirect and chronic character. Just what rôle these principles play in the genesis and perpetuation of renal hypertension remains a matter for further study.

This description of the humoral agents potentially involved in renal hypertension may be concluded with a consideration of the possible rôle of the adrenal cortical steroids, particularly those with the properties of desoxycorticosterone. On the clinical level the association of adrenal cortical overactivity in Cushing's syndrome with hypertension and nephrosclerosis is well established. Evidence of an experimental character has been provided by two types of procedures, ablation of the adrenals in animals with renal hypertension, and administration of desoxycorticosterone acetate (DOCA) or the induction of adrenal cortical hyperactivity.

Adrenalectomy usually results in the prompt disappearance of hypertension in dogs with renal hypertension and prevents its development following constriction of the renal arteries. A possible relation of these phenomena to the renin mechanism was indicated by the observation that although the renin content of kidneys of adrenalectomized dogs remains normal, there is a progressive fall in hypertensinogen which can be restored by the administration of DOCA. This is the basis for the suggestion that the inability of the adrenalectomized animal to maintain the hypertensive state

might in part be due to reduction in hypertensinogen, the formation of which in the liver may be dependent upon adrenal cortical function. It has also been found that kidneys from adrenalectomized animals lose the capacity to form VEM and that this function can be restored by DOCA or adrenal cortical extracts. Adrenalectomy also results in a progressive reduction in the response of the terminal vascular bed to the intravenous administration of VEM. Thus, removal of the adrenals results in certain modifications of two of the humoral systems which are suspect in renal hypertension.

Loeb was the first to report the hypertensive effects of DOCA given together with salt to patients with Addison's disease. Later studies in his clinic by Perera and co-workers showed similar effects in non-Addisonian and hypertensive subjects, an observation which has been confirmed by Schroeder. Selye has reported the development of hypertension and nephrosclerosis following DOCA in rats receiving high salt supplements; these effects could be prevented by the simultaneous administration of ammonium chloride. He also observed hypertension to follow the exposure of rats to a variety of stress situations which lead to chronic adrenal cortical hyperactivity. From these and other observations Selye would assign a primary rôle to the adrenal cortex in the genesis of hypertension. He postulates that a variety of appropriate stress situations, which lead through the anterior pituitary to adrenal cortical hyperactivity, would release large amounts of corticosteroids with properties similar to DOCA; these corticosteroids would then directly increase the production of pressor agents by the kidney, with resultant hypertension and nephrosclerosis.

There can be no doubt about the importance of the adrenal cortex for regulation of blood pressure; hypertension cannot be maintained in its absence. What remains for future study to establish is its exact rôle, whether as the prime mover or as an essential component of a complex system

which can be activated or interrupted at a number of points.

The significance of these developments on the experimental level is in large measure dependent upon their relevance to the problem of essential hypertension in man, and it is on this point that we encounter the greatest divergence of opinion. Goldblatt has summarized the many resemblances between experimental renal and essential hypertension which have led him to conclude that a fundamental similarity exists between the two conditions. Favorable to their identity is the existence of a chronic benign and a malignant phase of experimental renal hypertension with retinal and renal excretory changes comparable to those seen in the analogous stages of essential hypertension in man. The hemodynamics are also similar in both conditions. Furthermore, occasional cases are encountered in man in which unilateral renal disease, due to vascular anomalies or chronic inflammatory disease, is associated with hypertension corrected by removal of the involved kidney.

The status of the relation of the renin-hypertensin system to essential hypertension is essentially the same as for experimental renal hypertension. Its implication is favored by the fact that administration of hypertensin to animals and man elevates both systolic and diastolic pressures and produces changes in renal blood flow comparable to those found in essential hypertension. Less conclusive are the results of the assay for renin. As pointed out in Dexter's review, although renin had been found in the blood for short periods of time in a few instances of acute hypertension resulting from glomerulonephritis and eclampsia, efforts to detect renin in chronic essential hypertension had been as uniformly unsuccessful as in the chronic stage of experimental renal hypertension. However, since Dexter's review was written, Fasciolo and Taquini have developed a more sensitive method for renin assay by means of which they were able to demonstrate its presence in chronic

essential hypertension but in no greater amounts than in normotensive subjects.

Recently new evidence of a similarity between these two conditions has been provided by the observations of Shorr and Zweifach that the high concentrations of VEM and VDM previously noted in the blood during the chronic stage of renal hypertension in dogs are also regularly present in chronic essential hypertension in man.

The opposite viewpoint has been vigorously presented in these seminars by Goldring and in a review in this Journal by Smith. They point out that those instances in which unilateral renal disease is responsible for hypertension represent only a small fraction of the cases of essential hypertension. Furthermore, there is no greater incidence of hypertension in urologic conditions associated with unilateral renal disease than in the general population. The analysis by Chasis and Redish of the renal blood flow and excretory function of both kidneys in essential hypertension revealed no significant differences to justify the inference that a unilateral reduction of renal blood flow could be responsible for the initiation of hypertension.

They do, however, recognize that the generalized increase in peripheral resistance in essential hypertension, the increased constriction of the renal blood vessels, including both afferent and efferent glomerular arterioles and its reversibility by pyrogenic agents, as well as the persistence of impaired renal blood flow following sympathectomy, all make it necessary to assume the participation of a humoral pressor agent. But they find it difficult to relate this humoral pressor agent to the kidney in terms of the renal hypertension experiment of Goldblatt. They point out that although there is usually some reduction in blood flow and renal excretory function, essential hypertension can exist typically with no significant impairment of either index. Thus, if the pressor agent is of renal origin and if renal ischemia is essential for its production, there is no present knowledge as

to the way in which ischemia is initiated. That it does not result from primary vascular disease is evident from the many instances of essential hypertension unaccompanied by vascular disease. The link which they regard as essential for establishing the identity of experimental renal and essential hypertension is therefore missing. It is, for Smith, "illogical to suppose that at one moment humoral agents are operating to reduce renal blood flow and then at the next moment suppose that the reduction in blood flow is the reason for the appearance of these agents in the blood." If hypertensive disease is the result of myriads of clamps on renal arterioles in consequence of arteriolar sclerosis, then the arteriolar disease which remains unexplained is the primary event and not limited to the kidney. In short, the kidney appears to be the victim rather than the culprit although once involved it may play an accessory rôle.

Goldblatt's position with respect to these objections is as follows: To regard the experimental type of hypertension as necessarily dissimilar to essential hypertension because the main renal artery of humans with hypertension is not frequently stenotic is to misinterpret the main purpose and significance of the experimental procedure. The constriction of the main renal artery was an expedient resorted to as most likely to reproduce the circulatory disturbance of the kidney resembling the most probable effect of *intrarenal* stenosing arterial and arteriolar sclerosis. Those instances in man in which unilateral kidney disease leads to hypertension are therefore not to be regarded as etiologically typical but rather as important evidence that some type of alteration in renal blood flow can also cause a condition in man similar in its clinical manifestations to typical essential hypertension. There is no good *a priori* reason why experimental constriction of the main renal artery should not be considered capable of reproducing the functional state of the human kidney in essential hypertension. The ultimate decision must rest upon facts, of which an impressive number

have been accumulated which favor a similarity between experimental renal and essential hypertension and hence the primary renal origin of the latter.

However, to the problem posed by Smith as to the primary or secondary character of the changes in the renal circulation in essential hypertension there is admittedly no present answer. Indeed this question represents the core of the difficulty in reconciling these divergent viewpoints. Goldblatt's present position may be interpreted as favoring some antecedent intrarenal arterial and arteriolar sclerosis as the initiating factor for the renal humoral mechanism. Even were these renal vascular changes part of a more generalized vascular process, he suggests that their significance for peripheral vascular resistance would be greater because of their relation to the renal pressor mechanism for which no counterpart has as yet been found in other tissues. Thus for Goldblatt the cause of vascular disease now becomes the most important problem for future investigation of the pathogenesis of hypertension.

It is possible that both positions are somewhat too rigidly formulated as regards the potential primary rôle of the kidney in essential hypertension. There may be a middle ground between antecedent renal vascular disease and renal vasospasm secondary to extrarenal pressor agents which might profitably be explored. Such an alternative is advanced in the statement by Smith and co-workers that "the possibility cannot as yet be excluded that the appearance of pressor and cytotoxic substances in the blood follows a metabolic disorder in the kidney or other organs and is wholly independent of renal ischemia." This statement does not, of course, exhaust the many possibilities inherent in this provocative suggestion as, for example, the deterioration of an enzymatic system regulating a renal humoral mechanism through repeated exposures to brief periods of ischemia of, say, neurogenic origin, and the subsequent persistence of this metabolic disorder independent of sustained renal ischemia.

The full exploration of these possibilities will be feasible only when all the details are known not only of the intermediary metabolism of the renal-humoral mechanisms but also of the factors, intra- and extrarenal, by which their metabolism may be influenced. How far we are from this goal in the case of the renin system has already been indicated. However, some idea of the type of situation which may prevail might be gained from the still incomplete picture of the mechanisms governing the metabolism of the hepatorenal vasotropic factors, VEM and VDM. Each of these principles is formed under anaerobic, and inactivated or its formation inhibited under aerobic conditions, a situation analogous to the Pasteur reaction which restricts lactic acid formation by normal tissues to anaerobiosis. These reactions appear to be under enzymatic control; preliminary studies of the liver VDM inactivation system indicate the participation of a protein apoenzyme and a heat-stable, dialyzable co-enzyme whose effects can be reproduced by muscle adenylic acid. These reactions as a whole may be regarded as intracellular homeostatic systems by which the supply of VDM and VEM could be adjusted to the circulatory requirements of the organism.

However, this intracellular regulation of both anaerobic and aerobic phases of these systems in liver and kidney can be regularly disturbed by specific variations in environmental conditions. Thus, the VDM inactivation system of the liver undergoes deterioration during the hypoxia of that organ in irreversible shock as well as after a two-hour exposure to anoxia *in vitro*. It is also damaged in rats with nutritional cirrhosis due to low-protein, high-fat diets. A brief exposure of the kidney to anoxia *in vitro* results in a loss of the capacity to prevent the aerobic formation of VEM; more prolonged anoxia, *in vivo* and *in vitro*, causes a total loss of the ability to form VEM as does fasting or a low-protein diet. Adrenalectomy also abolishes VEM formation; this can be restored by DOCA or adrenal cortical extracts but not by salt.

Of particular interest in the problem of hypertension is the loss, following partial constriction of the renal artery, of the capacity of the kidney to inhibit the aerobic formation of VEM. This defect persists as long as the clamp is in place even though the normal oxygen consumption of the kidney, as determined *in vitro*, might suggest the return of an adequate supply of oxygen to the kidney *in vivo*. It is as a result of this defect that VEM appears in blood throughout the hypertensive syndrome, predominating in the acute phase, but accompanied by equivalent amounts of VDM during the chronic stage. Since studies by Bradley have shown that the hepatic blood flow in hypertension is unimpaired, liver hypoxia would not seem to be responsible for the release of VDM during the chronic stage. It is suggested that the stimulus may be the presence of abnormal amounts of the oppositely-acting VEM, an inference consistent with the dynamics of a homeostatic system. This last observation is of special interest as indicating, at least for this set of vascular principles, that other factors than ischemia may lead to derangements similar to those caused by ischemia.

The derangements of the renal VEM mechanisms by short periods of anoxia call to mind the attempts to induce hypertension by repeatedly subjecting the kidney to brief periods of ischemia on the theory that irreversible changes in the renal humoral mechanisms might eventually result. Unfortunately, interpretation of the positive results reported is clouded by the damage usually sustained by the renal blood vessels from the manipulation involved. In man, also, increasing attention is being focused on the consequences for hypertension of repeated exposures to the transitory reduction in renal blood reported to result from a variety of painful or emotionally distressing stimuli. In this connection the possible relation of the intrarenal vascular shunts, studied by Trueta and co-workers, to renal cortical ischemia is of considerable interest but still remains to be established.

These observations on the VEM-VDM systems are set forth in some detail for the suggestions inherent in them of the ways by which the renin system or any other renal-humoral vasoactive system might be similarly studied. The ultimate goal of such an investigation may be reached only when all of the reactions involved are understood, the modifying circumstances, intrinsic and extrinsic, recognized and the active principles and enzyme systems concerned isolated in pure form. Only then may it be possible to assess conclusively the rôle of the renal-humoral systems in hypertension and to explore the therapeutic avenues which might be opened, secure from the objections to which previous efforts with impure materials have been so vulnerable.

It would extend this already lengthy survey unduly to enter into the many controversial aspects of the present medical and surgical treatment of essential hypertension. The reader will find them vigorously set forth in the seminars by Kempner, Schroeder, Smithwick, Goldring and the review by Smith. Here he will find every shade of opinion as to their effectiveness, from the highly favorable to the verdict of "experimentation based on desperation." Such differing judgments by students observing much the same material must certainly in considerable measure depend upon the particular yardstick employed, whether cure or amelioration. Whatever the standards, they should be applied with caution lest, on the one hand, therapeutic endeavors be discouraged by setting the sights too high or, on the other, scientific judgment give way to an indiscriminating pragmatism. A good deal of criticism has with reason been levelled at the lack of adequate control observations in many therapeutic studies. An adequate base line, such as is outlined by Perera's studies, is essential for the evaluation of therapy in a condition such as hypertension which is so prone to non-specific spontaneous variations, particularly in regard to the level of the blood pressure, the index most commonly used. It would seem unwise, however, to neglect

the potential significance of any evidence, provided it is soundly documented, even though it is based upon partial relief and on the response of only a proportion of the patients treated. The syndrome is highly complex; it undoubtedly varies in the degree to which one or another element predominates and in the extent to which various derangements are reversible at any stage in its evolution.

It would be a happy circumstance indeed to be able to conclude this survey of experimental renal and essential hypertension by a synthesis of what is known into a structure whose pattern, although incomplete, is nevertheless architecturally harmonious. As it stands, however, the foundations are still fragmentary, the main arch still lacks a keystone and there is no unanimity about the grand design. In spite of this a structure is slowly but steadily taking form and it is a presage of its eventual soundness that each brick, stone and girder is being rigorously tested before it is put in place. And in this process we must not undervalue the constructive force of the creative imagination just because it has fashioned a variety of designs from the same raw material.

The richness of the raw material which has been accumulated over the past fifteen years and the avenues which have been opened for further exploration should, with reason, temper our reaction to the one conclusion about which there is general agreement—that at present the origin of essential hypertension remains unknown. That this conclusion has been accepted as a challenge rather than a sign of defeat is evident from the intensification of the efforts which are being directed at this problem whose urgency hardly needs emphasizing. Smith, from a survey of data supplied by

the Bureau of the Census, calculated that about one million persons above the age of forty-five die in this country every year; of this number approximately 450,000 die of one or another sequela of cardiovascular renal disease, nearly five times as many as die of cancer. A large fraction of cardiovascular renal disease is hypertensive in origin, presenting us with what is perhaps medicine's major problem. It is regrettable that compared with some other areas of medicine, research in cardiovascular disease has hitherto received support in a measure that is so poorly commensurate with its importance. There are, however, encouraging signs that this situation is on the way to being corrected in the increased support which is becoming available from private and public sources. The new National Heart Institute, which has been set up under the direction of Dr. C. J. Van Slyke, is the most recent expression of the increasing awareness of public responsibility for this major aspect of the health of the nation.

In this survey it has not been feasible to document the contents with bibliographic references or to cite all the meritorious studies in the very voluminous literature. Its main purpose has been to assist the reader in steering a course through the maze of data, frequently of a conflicting character, which has accumulated and, more especially, to send him back to the seminars themselves. The interested reader may also consult with profit the excellent translation by Dexter of the monograph by Braun-Menendez and co-workers on Renal Hypertension, the First Conference on Factors Regulating Blood Pressure, published by the Josiah Macy, Jr. Foundation, and the recent Symposium on Hypertension of the New York Academy of Sciences.

EPHRAIM SHORR, M.D.

The Hemodynamic Response of Man to Nor-Epinephrine and Epinephrine and Its Relation to the Problem of Hypertension*

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THE present study was undertaken in order to evaluate the possible rôle of the sympathetic nervous system in the mechanism of essential hypertension, employing the response to *l*-nor-epinephrine and *l*-epinephrine as a means of investigation.

NOR-EPINEPHRINE

Nor-epinephrine (nor-adrenaline, arterenol, amino-ethanolicatechol) is a primary amine identical with epinephrine except for the absence of a methyl group on the nitrogen atom. (Fig. 1.) It was first synthesized by Stolz³⁷ in 1904. Recently it has been suggested as a possible precursor of epinephrine *in vivo*⁵ since it has been shown that methylation occurs readily in the body.¹¹ The levo-isomer, possessing approximately twice the activity of the optically inactive preparation, became available in 1948 following resolution of the racemic mixture by Tainter and his group.³⁸

The consistency with which the actions of nor-epinephrine reproduce those of stimulation of sympathetic efferent nerves has led competent investigators to the conclusion that it may be sympathin E, as first suggested by Baerq.² In support of this hypothesis Stehle and Ellsworth³⁶ and Greer and his co-workers²⁰ demonstrated

the striking similarity between the effects of nor-epinephrine and those produced by stimulation of the hepatic sympathetic nerves. These observations have been confirmed by von Euler^{12,13} and Gaddum and Goodwin.¹⁸

The strongest evidence in favor of this assumption was von Euler's demonstration in 1946 of a substance in mammalian adrenergic nerves indistinguishable from nor-epinephrine by biologic and crude chemical tests.^{12,13} The thoracic and lumbar sympathetic chain and the splenic periarterial nerves of cattle were particularly suitable sources and contained the equivalent of 10 to 25 μ g. of *d,l*-nor-epinephrine per Gm. of tissue. This substance differed from epinephrine in its blood pressure action following ergotamine. Ergotamine reverses the pressor effect of epinephrine but not of nor-epinephrine. This substance differed likewise from epinephrine in its action on the non-pregnant rat uterus in that relaxation was inconspicuous.

It has been assumed that each of the transmitters, epinephrine and nor-epinephrine, carries efferent or inhibitor functions exclusively. But this does not appear to be so because efferent functions are carried not only by nor-epinephrine but also by epinephrine. Epinephrine has been proved to be the transmitter of sympathetic excitation in

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certain areas, namely, the heart and the vessels of the skin.^{17,24}

Whereas epinephrine shows a complex of pharmacologic actions composed of both excitatory and inhibitor functions, in nor-epinephrine the excitatory functions prevail. Barger and Dale⁴ in 1910 demonstrated that introduction of a methyl radical into the amino group produced inhibitory actions in various sympathomimetic amines. The pressor effect of *d,l*-nor-epinephrine was greater than that of *d,l*-epinephrine, and the relaxation of the non-pregnant cat uterus was inconspicuous.

A recent study by West⁴⁰ gives a summary of previous investigations and a comparison of pharmacologic responses to nor-epinephrine and epinephrine. Tainter³⁸ found that the acute toxicity of intravenously injected *l*-nor-epinephrine in mice was only one third that of *l*-epinephrine. For equivalent pressor doses *l*-nor-epinephrine had a safety ratio (toxicity to pressor activity) which was four times that of *l*-epinephrine. No studies of nor-epinephrine in man have been published up to this time.

EPINEPHRINE

The classic pharmacologic conception of the pressor action of epinephrine is that it depends chiefly on intense vasoconstriction, the direct cardiac action being only accessory. The hypotensive action of epinephrine in small doses, reported as early as 1900²⁸ and extensively studied by Cannon and Lyman,⁸ has been generally regarded as of minor physiologic importance.

Starr and his co-workers³³ and Ranges and Bradley,³¹ using ballistocardiographic output determinations, found that subcutaneous administration of therapeutic amounts of epinephrine in man resulted in increased cardiac output, decreased peripheral resistance and diastolic pressure with only a small elevation of systolic tension. Starr attributed the observed drop of total peripheral resistance, which seemed to contradict common pharmacologic experience, to the subcutaneous route of

administration with resulting slow resorption of minute amounts of the drug.

McMichael and Sharpey-Schafer,²⁷ using the direct Fick method, observed an increased cardiac output after minute amounts of epinephrine insufficient to alter the

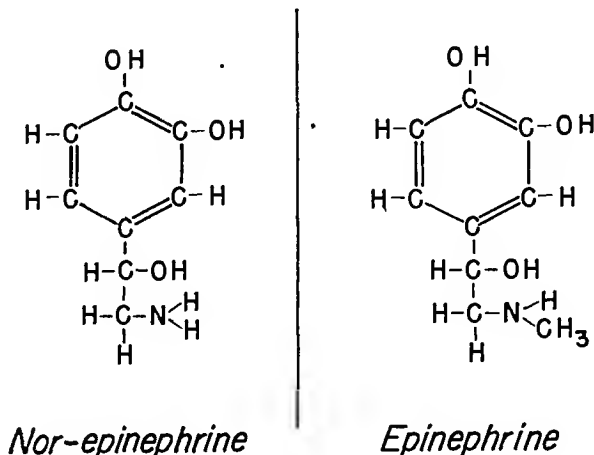


FIG. 1.

blood pressure, pulse rate or intra-auricular pressure, findings compatible with a fall in peripheral resistance. The studies on muscle blood flow in man by Allen, Barcroft and Edholm¹ show a significant vasodilator response during intravenous infusion of epinephrine in average doses of 10 μ g./min.

The results of these studies raise the question whether the doses used are comparable to a physiologic rate of release of epinephrine in man. In this case one would expect the vascular effect of epinephrine under physiologic conditions to be predominantly inhibitory.

A uniform increase of peripheral resistance has been commonly accepted to be present in essential hypertension.^{29,30,35} If essential hypertension is due to an increase of sympathetic activity in the arterial tree, it should be possible to reproduce its hemodynamics by an intravenous infusion of the sympathetic transmitter. This method was used by Fatheree and Hines¹⁵ who studied the changes in blood pressure and pulse rate following epinephrine infusion in normotensive and hypertensive subjects. Whereas elevation of diastolic pressure is a characteristic feature of essential hypertension, epinephrine caused only an in-

significant increase of diastolic blood pressure in normotensive subjects. The diastolic pressure was decreased in hypertensives. They attributed the concomitant rise of systolic blood pressure to increased cardiac activity and the relatively slight rise or decrease in diastolic pressure to peripheral vasodilation. As long as epinephrine was regarded as the only sympathetic transmitter this study would appear to exclude increased sympathetic activity as an important mechanism in essential hypertension. The recent evidence of the dual nature of the sympathetic chemical mediators^{3,12,13} made it desirable to re-investigate the problem.

METHODS

In preliminary studies the systemic blood pressure and pulse rate of twenty hospital patients without cardiovascular disease, fourteen patients with uncomplicated essential hypertension, one patient with chronic nephritis and one patient with chronic hypertensive cardiovascular disease in failure were observed during a continuous intravenous infusion of nor-epinephrine, epinephrine or a mixture of the two, the latter given only to normals. The solutions were made up to contain 4 micrograms of nor-epinephrine or epinephrine per ml. of saline. During the preliminary studies *d,l*-nor-epinephrine was used until *l*-nor-epinephrine became available.

With the patient at rest, normal saline was infused. When the arterial blood pressure and pulse became stabilized, a three-way stopcock was turned to the drug infusion which was first allowed to flow at the rate of 0.05 $\mu\text{g.}/\text{Kg.}/\text{min.}$ of the test substance. The highest amount of *l*-nor-epinephrine given in these experiments was 0.4 $\mu\text{g.}/\text{Kg.}/\text{min.}$ The pulse and systemic blood pressure, obtained by cuff, were observed about every two minutes. The dosage was regulated in such a manner as to obtain significant responses in normals and, on the other hand, to keep the pressure response in hypertensives below spontaneous peak levels.

In eight patients with normal blood pressures and three patients with uncomplicated hypertension, intra-arterial pressures and cardiac output determinations, using the direct Fick method, were obtained before and during such drug infusions. The mixed venous blood was

withdrawn anaerobically from an intracardiac catheter placed in the right or left pulmonary artery about 3 cm. from the bifurcation. The arterial blood was obtained from an indwelling arterial needle seated in either a brachial or femoral artery. The oxygen contents of these blood samples was determined immediately by the manometric method of van Slyke and Neill. Duplicate blood samples were required to check within 0.2 volumes per cent. The expired air was measured and collected in a Tissot spirometer and duplicate aliquot samples analyzed for oxygen and carbon dioxide in a Haldane apparatus. The systemic and pulmonary arterial pressures were recorded by Hamilton manometers immediately before and after each cardiac output determination and the mean pressures obtained by planimetric integration of the pressure tracings. The total peripheral resistance (TPR) expressed in dynes $\text{cm.}^{-5} \text{sec.}$ was calculated from the following formula:

$$\text{TPR} = \frac{\text{mean arterial pressure mm. Hg}}{\text{cardiac output L. per second}} \times 13.32^*$$

The value of the mean arterial pressure used in this calculation was the mean of the two observations made directly before and directly after the blood sampling for the cardiac output determination. These values rarely varied by more than 3 or 4 mm. of mercury.

The patients were studied in the postabsorptive state. All but one received 0.1 Gm. of sodium pentobarbital by mouth before reaching the laboratory. Immediately after introduction of the catheter into the pulmonary artery and placement of the intra-arterial needle an intravenous saline infusion was started. Usually within ten to fifteen minutes following these manipulations the patients were in a sufficiently stable resting state to make the first group of control measurements. A second group of baseline observations were made following a fifteen to thirty-five-minute rest period. Thereupon, epinephrine or nor-epinephrine was given as previously described at a rate determined by a previous sensitivity test. The pulse rate and blood pressures by cuff were checked to select a significant blood pressure increase with a constant level for further observations. The first Hamilton manometer pressure recordings and cardiac output determinations were obtained

* 13.32 = specific gravity of mercury.

TABLE I

CARDIOVASCULAR RESPONSE OF EIGHT NORMOTENSIVE AND THREE HYPERTENSIVE PATIENTS TO INFUSIONS OF *l*-EPINEPHRINE AND *l*-NOR-EPINEPHRINE

I. Patients without Cardiovascular Disease: During successive infusions of *l*-epinephrine, *l*-nor-epinephrine, and *l*-nor-epinephrine + *l*-epinephrine

Case	Time	State, Drug	Dose μg./ kg./ min.	Pulse	Mean Pul- monary Arterial Pressure (mm. Hg)	Systemic Arterial Pressure			Ventila- tion L./min./ sq. m.*	Oxygen Intake cc./min./ sq. m.†	Arterio- venous Oxygen Differ- ence (vol- umes per cent)	Cardiac Output L./min.	Total Peri- pheral Resist- ance (dynes cm. ⁻⁵ sec.)
						Sys- tolic	Dias- tolic	Mean					
						mm. Hg	mm. Hg	mm. Hg					
I. J. S., twenty- six yr., male; body surface, 1.81 sq. m.	9:40	rest	64	14	120	68	86	2.9	144	3.5	7.46	922
	9:54	rest	60	14	121	70	88	3.1	145	3.9	6.72	1030
	10:14	<i>l</i> -epinephrine fourteen minutes	0.15	78	22	147	72	96	4.1	176	2.4	13.30	577
	10:35	rest	60	14	133	76	94	2.7	142	4.1	6.24	1205
	10:56	<i>l</i> -nor-epinephrine fourteen minutes	0.15	48	19	162	91	115	3.0	143	5.0	5.18	1785
	11:13	<i>l</i> -nor-epinephrine <i>l</i> -epinephrine twelve minutes	0.15 0.15	58	25	174	83	111	3.6	168	3.3	9.22	960
II. T. R., thirty- seven yr., male; body surface, 1.84 sq. m.	9:28	rest	68	10	141	71	95	3.0	111	3.2	6.33	1197
	9:50	rest	68	12	143	74	97	3.3	126	3.8	6.09	1270
	10:11	<i>l</i> -nor-epinephrine twelve minutes	0.16	53	18	191	90	122	4.0	153	3.9	7.20	1354
	10:26	<i>l</i> -nor-epinephrine <i>l</i> -epinephrine ten minutes	0.15 0.15	78	20	172	75	105	4.6	184	2.9	11.68	714
	10:43	<i>l</i> -epinephrine eleven minutes	0.16	96	14	143	66	91	4.8	195	2.5	14.37	500
	11:17	rest thirty minutes	80	9	125	69	88	4.3	178	4.4	7.46	942
III. E. G., thirty yr., male; body surface, 1.74 sq. m.	9:45	rest	78	16	124	78	98	4.2	138	3.4	7.04	1102
	9:57	rest	72	16	120	75	94	4.7	166	3.5	8.23	909
	10:16	<i>l</i> -epinephrine thirteen minutes	0.25	72	25	180	87	118	6.2	206	2.3	15.56	601
	10:40	rest	68	16	122	81	101	3.9	140	3.3	7.39	1090
	10:56	<i>l</i> -nor-epinephrine twelve minutes	0.25	50	22	184	106	138	3.9	140	4.3	5.68	1915
IV. C. G., forty- five yr., male; body surface, 1.81 sq. m.	9:42	rest	62	12	120	62	84	3.4	140	4.1	6.18	1086
	10:06	<i>l</i> -epinephrine fourteen minutes	0.30	68	22	162	65	98	4.9	182	3.0	10.97	714
	10:25	<i>l</i> -epinephrine thirty-seven minutes	0.28	86	20	164	70	101	5.8	189	2.3	14.82	545
	10:49	rest twenty-three minutes	72	10	118	63	85	4.3	177	3.8	8.43	808
	11:08	<i>l</i> -nor-epinephrine fifteen minutes	0.28	54	14	162	83	109	5.7	204	4.5	8.18	1060

During infusion of *l*-nor-epinephrine alone

V. B. H., twenty- five yr., male; body surface, 2.00 sq. m.	10:20	rest	87	17	120	71	90	4.8	183	3.8	9.61	748
	10:55	rest	75	18	132	80	99	5.2	194	3.8	10.20	776
	11:25	<i>l</i> -nor-epinephrine twenty-two minutes	0.11	60	21	160	84	113	6.2	220	4.1	10.73	838
	11:35	<i>l</i> -nor-epinephrine thirty-two minutes	0.125	58	20	156	85	110	7.1	228	4.5	10.10	871

TABLE I (Continued)

Case	Time	State, Drug	Dose μg./ Kg./ min.	Pulse	Mean Pul- monary Arterial Pressure (mm. Hg)	Systemic Arterial Pressure			Ventila- tion L./min. /sq. m.*	Oxygen Intake cc./min. /sq. m.†	Arterio- venous Oxygen Differ- ence (vol- umes per cent)	Cardiac Output L./min.	Total Peri- pheral Resist- ance (dynes cm. ⁻⁵ sec.)
						Sys- tole	Diás- tole	Mean					
						mm. Hg	mm. Hg	mm. Hg					
vi. S. T., Forty- eight yr., male; body surface, 1.88 sq. m.	9:45	rest	92	5	132	78	97	5.8	149	3.7	6.38	1206
	9:59	rest	88	5	140	82	102	4.8	136	3.8	5.66	1440
	10:27	<i>l</i> -nor-epinephrine fourteen minutes	0.16	72	17	168	92	120	4.3	159	4.0	6.30	1518
	10:42	<i>l</i> -nor-epinephrine twenty-nine min- utes	0.12	72	17	176	94	125	7.2	198	3.9	8.03	1240
vii. F. P., twenty-eight yr., male; body surface, 1.85 sq. m.	9:40	rest	67	7	114	68	86	2.8	109	3.7	4.71	1453
	9:53	rest	68	7	117	68	89	3.0	118	3.5	5.40	1317
	10:30	<i>l</i> -nor-epinephrine twenty minutes	0.24	52	11	165	90	118	3.5	143	4.6	4.95	1900
	10:45	<i>l</i> -nor-epinephrine thirty-five min- utes	0.19	59	9	161	89	118	4.2	164	4.4	5.98	1570
viii. E. B., twenty-two yr., male; body surface, 1.85 sq. m.	9:35	rest	91	16	107	68	79	3.9	148	3.5	7.82	806
	9:48	rest	92	19	108	72	80	3.4	144	3.4	7.82	818
	10:15	<i>l</i> -nor-epinephrine fifteen minutes	0.40	58	38	156	93	114	4.5	170	5.0	6.30	1448
	10:30	<i>l</i> -nor-epinephrine thirty minutes	0.30	63	34	160	95	118	4.5	175	4.0	8.08	1168

II. Patients with Essential Hypertension: During infusion of *l*-epinephrine and, in one case, *l*-nor-epinephrine

ix. A. B., forty- six yr., male; body surface, 1.95 sq. m.	2:13	rest	74	13	194	113	142	3.9	138	4.6	5.85	1920
	2:20	rest	72	14	189	111	139	3.8	141	4.4	6.24	1770
	2:44	<i>l</i> -epinephrine ten minutes	0.07	84	20	193	105	137	4.3	152	3.6	8.26	1315
	2:54	<i>l</i> -epinephrine twenty minutes	0.14	90	21	209	115	147	5.5	205	3.7	10.80	1080
	3:11	rest twelve minutes	84	13	193	118	144	4.3	176	4.8	7.15	1600
x. R. G., forty- four yr., female; body surface, 1.55 sq. m.	9:41	rest	60	4	255	115	156	2.5	132	4.3	4.75	2600
	9:52	rest	61	13	250	113	156	2.7	139	4.5	4.80	2580
	10:11	<i>l</i> -epinephrine eleven minutes	0.16	80	17	242	102	145	4.1	182	2.9	9.73	1180
	10:20	rest six minutes	74	13	229	98	138	3.3	154	3.8	6.27	1750
	10:47	rest thirty-three minutes	61	11	243	110	150	2.7	136	4.4	4.78	2490
xi. E. B., thirty- four yr., female; body surface, 1.54 sq. m.	9:57	rest	90	10	152	87	113	3.5	119	3.3	5.56	1608
	10:13	rest	90	9	152	88	113	3.5	121	3.8	4.93	1815
	10:32	<i>l</i> -epinephrine twelve minutes	0.11	108	12	150	79	106	4.3	153	2.6	9.04	928
	10:46	<i>l</i> -epinephrine twenty-seven minutes	0.20	119	12	155	79	107	4.7	171	2.6	10.10	842
	11:16	rest	104	11	132	74	94	3.8	139	3.2	6.67	846
	11:40	<i>l</i> -nor-epinephrine thirteen minutes	0.20	94	14	172	92	119	4.1	145	3.1	7.19	995

* Calculated as dry gas at 37°C. and 760 mm. barometric pressure.

† Corrected to 0°C. and 760 mm. barometric pressure.

after the infusion had been running eleven to twenty-two minutes. During the course of the experiments the patients received approximately 500 cc. of saline. During all but one of

during the preliminary nor-epinephrine infusion studies are summarized in Table III and the systolic pressure responses of the normal and hypertensive groups to differ-

TABLE II
RANGE OF CHANGE OF CERTAIN CARDIOVASCULAR FUNCTIONS DURING REST AND THE INFUSION
OF *l*-EPINEPHRINE AND *l*-NOR-EPINEPHRINE

Function	Fluctuation between Resting Values during Saline Infusion	Changes during Eleven to Fourteen Minutes of <i>l</i> -epinephrine Infusion in Doses of 0.15 to 0.30 $\mu\text{g.}/\text{Kg.}/\text{min.}$	Changes during Fifteen to Twenty-two Minutes of <i>l</i> -nor-epinephrine Infusion in Doses of 0.11 to 0.40 $\mu\text{g.}/\text{Kg.}/\text{min.}$	Changes after the Addition of Equal Amounts of <i>l</i> -epinephrine to <i>l</i> -nor-epinephrine Infusion
I. In eight normotensive patients				
Systolic pressure mm. Hg.	(8 cases) 12 to 1	(4 cases) +60 to +18	(8 cases) +62 to +28	(2 cases) +12 to -19
Diastolic pressure mm. Hg.	9 to 2	+12 to - 3	+25 to + 4	- 8 to -15
Mean systemic pressure mm. Hg.	9 to 2	+22 to + 3	+37 to +14	- 4 to -17
Mean pulmonary arterial pressure mm. Hg.	3 to 0	+10 to + 5	+19 to + 5	- 2 to - 6
Cardiac output L./min./sq. m. body surface.	0.68 to 0	+4.23 to +2.56	+0.61 to -1.19	+2.23 to +2.42
Total peripheral resistance dynes cm^{-5} sec.	234 to 36	-308 to -453	+825 to +62	-825 to -640
Pulse rate min.	13 to 0	+16 to 0	+ 6 to -34	+25 to +10
II. In three patients with uncomplicated essential hypertension				
Systolic pressure mm. Hg.	(3 cases) 5 to 0	(3 cases) +20 to - 8	(1 case) +40	
Diastolic pressure mm. Hg.	2 to 1	+ 4 to -13	+18	
Mean systemic pressure mm. Hg.	3 to 0	+ 8 to - 2	+25	
Mean pulmonary arterial pressure mm. Hg.	1	+ 6 to + 3		
Cardiac output L./min./sq. m. body surface.	0.41 to 0.03	+3.66 to +1.03	+0.34	
Total peripheral resistance dynes cm^{-5} sec.	207 to 20	-422 to -973	+149	
Pulse rate min.	2 to 0	+19 to +12	-10	

the cardiac output studies *l*-nor-epinephrine was used.

RESULTS

The full data obtained during the cardiac output studies on both groups of patients are summarized in Table I. The range of changes observed in the most significant cardiovascular functions of the two groups of patients during the initial period of rest and following the various drug infusions are presented in Table II. The data obtained

ent infusion rates of the drug are presented in Figure 2.

OBSERVATIONS OF PATIENTS WITH NORMAL BLOOD PRESSURE

Cardiovascular Response to Epinephrine Infusion. Upon intravenous infusion of epinephrine in doses of 0.15 to 0.30 $\mu\text{g.}/\text{Kg.}/\text{min.}$ for a period of eleven to fourteen minutes the following hemodynamic changes were observed in four patients with normal blood

pressures: (1) A striking increase of cardiac output in all cases (78 to 98 per cent of the resting value); (2) a significant rise of the systemic systolic pressure associated with an insignificant change of the diastolic pressure in all cases; (3) a slight rise of the

persistent elevation of the pulse rate, oxygen consumption and cardiac output as well as by the lowered total peripheral resistance.
Comment. The cardiovascular response of the four subjects given an intravenous infusion of epinephrine was uniform and

TABLE III

RESTING LEVELS AND INCREASES OF SYSTEMIC ARTERIAL PRESSURES OBSERVED DURING *l*-NOR-EPINEPHRINE INFUSION IN A GROUP OF NORMOTENSIVE AND A GROUP OF HYPERTENSIVE PATIENTS

	Normotensive Group				Hypertensive Group			
	No. Cases	Mean	S.D.	Range	No. Cases	Mean	S.D.	Range
I. Resting Levels								
Systolic pressure mm. Hg.....	23	115	9.5	100-137	21	191	40.5	127-263
Diastolic pressure mm. Hg.....	23	70	7.7	54- 84	21	114	19.7	81-151
Mean pressure mm. Hg.....	23	85	7.9	73-100	21	139	25.3	96-179
II. Increase of Pressures with Increasing Doses of <i>l</i> -nor-epinephrine								
0.05-0.07 µg./Kg./min.								
Systolic pressure mm. Hg.....	12	8.4	6.0	0-23	21	30.0	19.5	0-65
Diastolic pressure mm. Hg.....	12	9.4	5.4	0-19	21	10.6	6.5	0-32
Mean pressure mm. Hg.....	11	7.3	3.4	0-13	21	16.7	10.1	0-43
0.10-0.13 µg./Kg./min.								
Systolic pressure mm. Hg.....	14	21.7	9.1	8-44	13	43.5	10.8	13-88
Diastolic pressure mm. Hg.....	14	13.6	7.0	4-25	13	17.3	8.3	5-34
Mean pressure mm. Hg.....	14	16.3	5.8	10-31	12	27.0	12.0	8-51
0.20-0.25 µg./Kg./min.								
Systolic pressure mm. Hg.....	14	38.0	9.0	6-56				
Diastolic pressure mm. Hg.....	14	22.0	8.6	5-34				
Mean pressure mm. Hg.....	14	26.5	11.2	5-42				

mean arterial pressure in three cases; (4) a sharp drop of the total peripheral resistance in every case; (5) a moderate rise of pulse rate in three cases and (6) a significant rise of the mean pulmonary arterial pressure.
The epinephrine infusion was continued at the same dosage for a thirty-seven-minute period in Case iv, at which time a further increase of the cardiac output and drop of the total peripheral resistance was noted. Furthermore, it is of interest that twenty-three minutes after termination of the epinephrine infusion and an appreciable time after the return of the systemic arterial pressures to normal limits an epinephrine effect was still present as judged by the

striking. It is evident that epinephrine, under the conditions of these experiments even with doses causing significant hypertension, acts as an overall vasodilator drug and a powerful cardiac stimulant. It should be noted, however, that the patients receiving the largest doses presented evidence of cutaneous vasoconstriction, i.e., pallor and a subjective sensation of cold.
Cardiovascular Response to Nor-Epinephrine. In those preliminary experiments in which only the blood pressure and pulse rate were determined an increase of both diastolic and systolic systemic arterial pressures associated with a slowing of the pulse was noted. During the infusion of 0.05 to 0.07 µg./Kg./min. of nor-epinephrine there was

an average rise of systolic pressure of 8 mm. Hg; increasing the dose to 0.10 to 0.13 $\mu\text{g./Kg./min.}$, the average rise was 22 mm. Hg; finally when 0.2 to 0.25 $\mu\text{g./Kg./min.}$ was infused, the average rise of systolic pressure was 38 mm. Hg. (Table III, Fig. 2.)

The bradycardia appears to be of vagal origin since it was abolished by atropine in three cases. The relative lack of subjective symptoms even in the presence of high systolic pressures is noteworthy. The following hemodynamic changes were observed

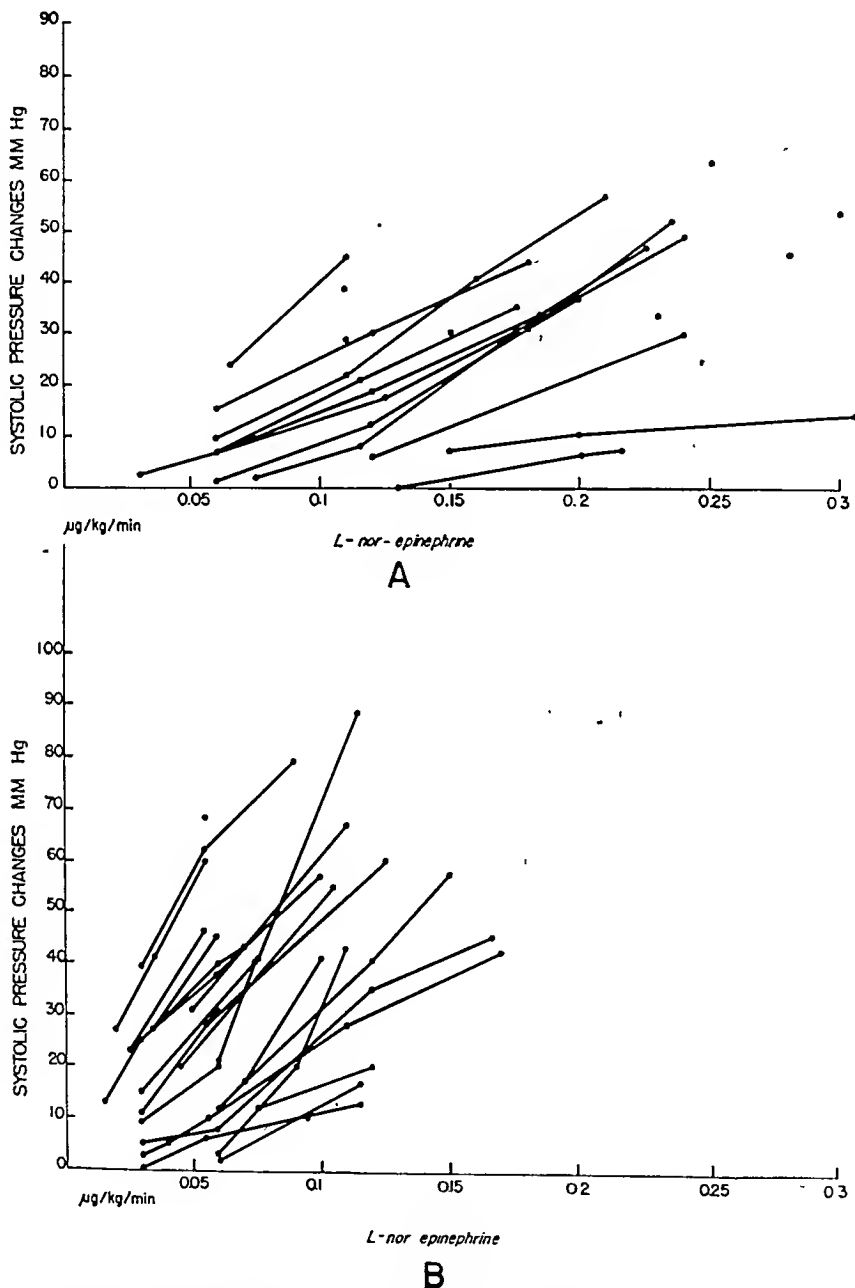


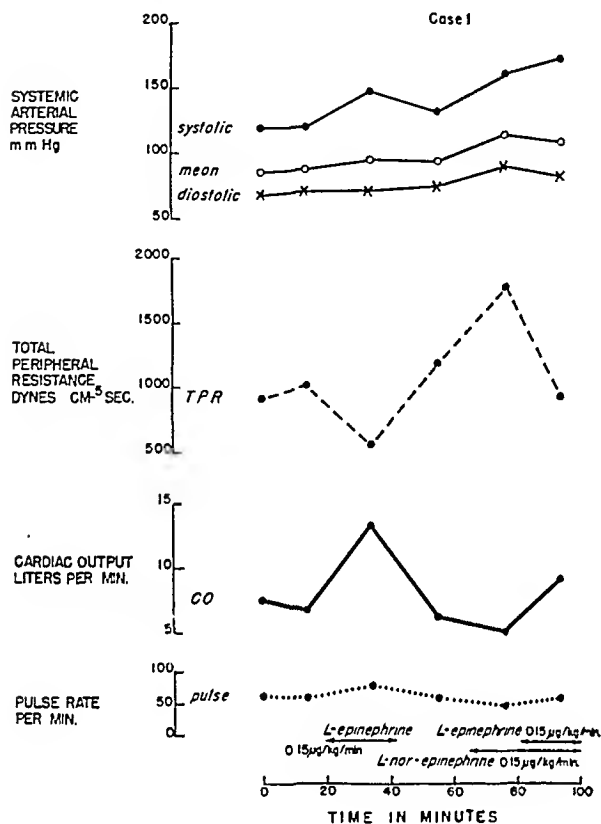
FIG. 2. The systolic pressure responses to increasing doses of *l*-nor-epinephrine: A, normotensive group; B, hypertensive group.

The minimum amount of nor-epinephrine required to produce a blood pressure elevation is variable in patients without cardiovascular disease but was on the average of 0.05 $\mu\text{g./Kg./min.}$ (Table III.)

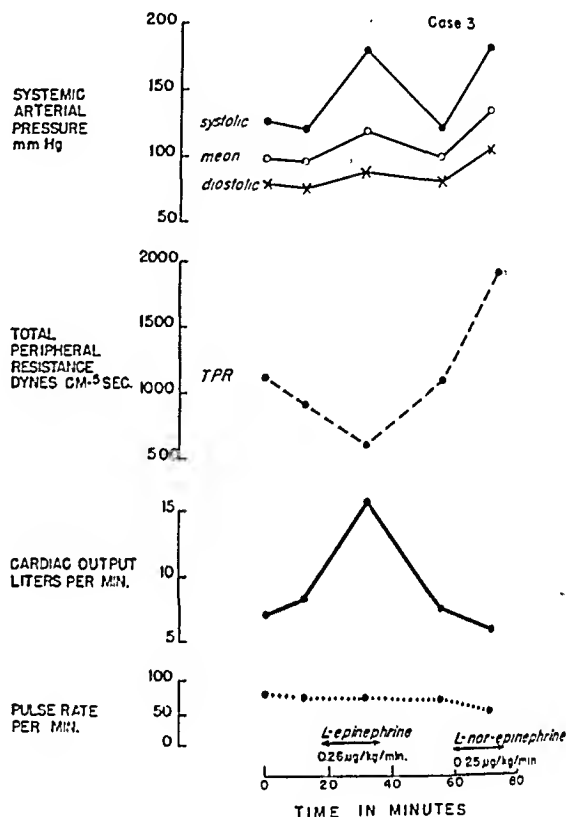
in eight subjects during the cardiac output studies following intravenous infusion of nor-epinephrine; in doses ranging from 0.11–0.40 $\mu\text{g./Kg./min.}$ for a period of fourteen to twenty-two minutes: (1) An

unchanged or a moderate decrease of the cardiac output in seven cases. (The cardiac output of Case II rose by 18 per cent.) (2) A significant rise of systolic systemic arterial pressure in all cases associated with a significant rise of diastolic pressure in all

no appreciable hemodynamic change was noted. In Cases VI through VIII in which the dosage was decreased an increase of cardiac output associated with relatively minor pressure changes resulted in a significant fall of the total peripheral resist-



3



4

FIG. 3. The hemodynamic changes observed in Case 1 during the successive infusion of *l*-epinephrine, *l*-nor-epinephrine and a combination of the two substances.

FIG. 4. The hemodynamic changes observed in Case 3 during the successive infusion of *l*-epinephrine and *l*-nor-epinephrine.

but the two patients who received the smallest doses. (3) A significant rise of the mean systemic arterial pressure in all cases. (4) A striking increase of total peripheral resistance in five cases. In no case was a drop observed. (5) A significant decrease of pulse rate in all but one case. (6) A significant rise of mean pulmonary arterial pressure in all cases.

In Cases V through VIII the nor-epinephrine infusion was continued for as long as twenty-nine to thirty-five minutes. In Case V in which the dosage was increased from a very low to a moderate amount

ance; this, however, did not reach resting values.

Cardiovascular Response to a Combination of Nor-Epinephrine and Epinephrine. In Cases I and II equal amounts of epinephrine were added to the nor-epinephrine infusion. The response to the combination of the two substances was: (1) a slight fall of mean arterial pressure; (2) a striking increase of cardiac output; (3) a sharp fall of the total peripheral resistance from the elevated levels during infusion of nor-epinephrine alone.

Two typical experiments are presented in Figures 3 and 4. Figure 3 represents the changes observed during rest and the successive infusions of equal doses of epinephrine, nor-epinephrine and a mixture of the two substances. During the infusion of 0.15 $\mu\text{g./Kg./min.}$ of epinephrine the systolic pressure rose from 121 to 147 mm. Hg while the diastolic pressure remained unchanged. The cardiac output doubled and the total peripheral resistance fell from 1,030 to 577 dynes $\text{cm.}^{-5} \text{ sec.}$, indicating an overall vasodilatation. Nor-epinephrine caused an increase of systolic and diastolic pressure from 133/76 to 162/91 mm. Hg, with a 17 per cent drop of cardiac output and a rise of total peripheral resistance from 1,205 to 1,785 dynes $\text{cm.}^{-5} \text{ sec.}$, indicating an overall vasoconstriction. Finally, when equal amounts of epinephrine were added to the nor-epinephrine infusion, there was little change in blood pressure; the cardiac output increased from 5.18 to 9.22 L. per minute, and the total peripheral resistance dropped to 960 dynes $\text{cm.}^{-5} \text{ sec.}$, indicating epinephrine—nor-epinephrine antagonism.

Figure 4 presents similar results obtained during a more significant hypertension induced by higher doses of the two substances. The infusion of a dose of 0.25 $\mu\text{g./Kg./min.}$ of epinephrine caused a blood pressure rise from 120/75 to 180/87 mm. Hg, associated with an increase of cardiac output from 8.23 to 15.56 L. per minute and a drop of total peripheral resistance from 909 to 601 dynes $\text{cm.}^{-5} \text{ sec.}$ The infusion of an equal amount of nor-epinephrine, which caused a blood pressure rise from 122/81 to 184/106 mm. Hg, was associated with a drop of cardiac output from 7.39 to 5.68 L. per minute and rise of total peripheral resistance from 1,090 to 1,915 dynes $\text{cm.}^{-5} \text{ sec.}$

Comment. From these findings the following conclusions may be drawn: (1) The primary action of nor-epinephrine is to produce an intense overall vasoconstriction and (2) this vasoconstriction action is com-

pletely blocked by the simultaneous administration of equal doses of epinephrine.

This antagonistic action of epinephrine to the nor-epinephrine effect amply explains the less uniform cardiovascular response of the patients to a small dose of nor-epinephrine. In such complicated experiments, necessitating the presence of five or six observers and a considerable amount of equipment, it may be impossible to prevent some patients from experiencing mild anxiety. The hemodynamic response to anxiety, as Hickam and his co-workers²² have recently shown, is in some cases similar to that obtained with small doses of epinephrine. Likewise, the observation of a moderate increase of cardiac output and consequent lowering of the peripheral resistance after a prolonged period of nor-epinephrine infusion, as seen in Cases VII and VIII, may be ascribed to the release of endogenous epinephrine in response to the prolonged procedure.

Epinephrine and nor-epinephrine resemble one another superficially by producing an increase of systolic and mean arterial pressures. Nor-epinephrine hypertension, however, is due to an increase of total peripheral resistance with no significant change or even a drop in cardiac output whereas epinephrine hypertension is the result of a significant increase of cardiac output in spite of a decrease of total peripheral resistance. These findings are demonstrated graphically in Figure 5. Finally, the vasoconstrictor action of nor-epinephrine can be blocked entirely by the simultaneous administration of equal amounts of epinephrine.

In normal subjects nor-epinephrine produces a type of hypertension that closely resembles that of essential hypertension. Both are characterized by a proportionate increase of systolic and diastolic pressure and by lack of tachycardia and of subjective symptoms. The uniform increase of total peripheral resistance is the only outstanding abnormality in both.

Nor-epinephrine hypertension is similar in its hemodynamics to the acute hyper-

tension produced by neosynephrine²³ and paredrinol.³⁴ It is noteworthy that Stead and Kunkel³⁴ who carefully studied paradrinol hypertension were impressed by its similarity to essential hypertension. There is no evidence, however, that these sub-

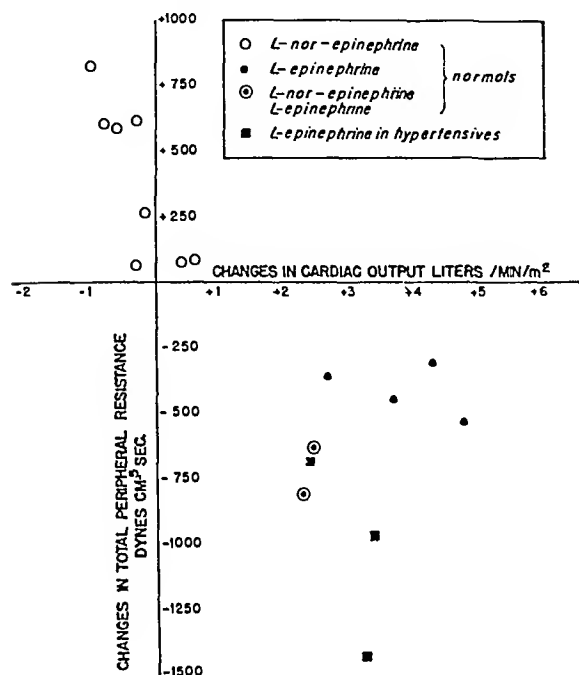


FIG. 5. The correlation between changes in cardiac index and changes in total peripheral resistance during the infusion of *L*-epinephrine and *L*-nor-epinephrine found in eight normotensive and three hypertensive patients.

stances occur naturally. Since an increase of stroke volume was observed, it may be concluded that the decrease of cardiac output is due to regulating mechanisms such as bradycardia rather than to cardiac failure. In one case the right auricular pressure was measured and found to be normal during nor-epinephrine administration.

Epinephrine, on the other hand, in a range of dosage comparable to the physiologic release was found to be an overall vasodilator. Generalized vasoconstriction in man, however, has been observed in patients with pheochromocytoma,¹⁹ a condition in which large amounts of circulating epinephrine are present. This type of response resembles the intense vasoconstriction commonly observed in animal experiments as indicated by the diminished

volume of organs. A hypotensive action of epinephrine following minute doses has been described^{8,28} but was not considered to have physiologic significance. Although the actual doses given in our experiments appear small, it is well known that man is more sensitive to epinephrine than laboratory animals. These doses, which were within and even beyond the physiologic range as shown by the marked pressor response, produced vasodilatation.

From our data it is impossible to state the site of epinephrine vasodilatation. Examination of the data of Allen et al.¹ indicates that the increase of blood flow is not confined to the muscles. There are three possible mechanisms by which epinephrine may cause vasodilatation: (1) direct action on the arteriolar muscle;¹⁰ (2) blocking of transmission through the sympathetic ganglia;^{7,26} (3) an epinephrine-nor-epinephrine antagonism. A depression of ganglionic transmission by epinephrine has only been observed following single massive doses.⁷ In fact during epinephrine infusion facilitation of ganglionic transmission has been reported.⁷ The demonstration in our experiments of an epinephrine-nor-epinephrine antagonism indicates that sympathetic tone, insofar as mediated by nor-epinephrine, may be abolished by epinephrine. This view makes it possible to reconcile the predominantly vasodilator response to epinephrine of unanesthetized man with the constrictor action seen in the vast majority of animal experiments and in cases of pheochromocytoma.

The increase of the mean pulmonary arterial pressure during epinephrine and during nor-epinephrine infusions is of great interest. It is impossible to decide from the data obtained in the present study whether this increase is due to back pressure from an elevated left auricular pressure or to vasoconstriction of the pulmonary vascular bed. Although a rise of left auricular pressure in dogs had been previously reported following large doses of epinephrine,²¹ recent animal experiments^{14,25} indicate that the left auricular pressure may not increase

following an injection of either substance and that the rise of pulmonary arterial pressure may be on the basis of vasoconstriction.

OBSERVATIONS ON PATIENTS WITH
UNCOMPLICATED ESSENTIAL
HYPERTENSION

Although only a limited number of patients with essential hypertension were studied, the results are so consistent that a preliminary report may be of interest.

Cardiovascular Response to Intravenous Infusion of Epinephrine. During the intravenous infusion of epinephrine in doses of 0.07 to 0.20 $\mu\text{g.}/\text{Kg.}/\text{min.}$ for a period of ten to twenty minutes the following hemodynamic changes were observed in three patients with essential hypertension: (1) A significant rise of the cardiac output in all cases; (2) a fall of the systolic and diastolic systemic pressure in two cases and an insignificant rise in one; (3) a fall of the mean arterial pressure in all cases; (4) a profound drop of the total peripheral resistance in all cases; (5) a significant rise of pulse rate in all cases; (6) a significant rise of the mean pulmonary arterial pressure in all cases.

Comment. From these limited observations it would seem that the hemodynamic response to epinephrine infusion of the hypertensive patients differs from that of the normotensive patients in the following respects: (1) A greater sensitivity to the vasodilator action of epinephrine characterized by a very marked lowering of the total peripheral resistance and (2) a tendency for the systemic arterial pressure to fall or remain relatively constant.

The striking similarity of this response with the epinephrine response of the normal group made hypertensive with nor-epinephrine should be noted. Furthermore, in Case XI twenty-four to forty-six minutes after stopping the epinephrine infusion, although the cardiac output had returned toward normal, a lowered peripheral resistance and a nor-epinephrine antagonism could be demonstrated. The results of the observations on the three patients are presented in Figures 6 to 8.

Cardiovascular Response to the Infusion of Nor-Epinephrine. During the nor-epinephrine sensitivity tests fourteen patients with uncomplicated hypertension showed an increased response of the systolic and mean arterial pressures when compared with the normotensive group. The diastolic pressure changes did not differ from the normal group. (However, during anesthesia an increased response of the diastolic pressure was observed in eight hypertensive patients.) In addition, normal responses were observed in two patients with essential hypertension tested at a time when their blood pressure was normal, one patient with chronic nephritis, one with cardiac failure due to hypertensive cardiovascular disease and one with generalized arteriosclerosis and hypertension. As may be seen in Figure 2 if dosage is plotted as abscissae and systolic blood pressure changes as ordinates, the concentration action curves of the hypertensive patients are shifted to the left of and show a steeper slope than those of the normotensive group. This increased sensitivity of the hypertensive patients obviously limited the dose administered. Although the groups are small, there is a statistically significant difference between the mean rise of the systolic and mean pressures of the two groups. (Table III.) The apparent decrease of the difference between the two groups with a dose of 0.1 to 0.13 $\mu\text{g.}/\text{Kg.}/\text{min.}$ may be due to the fact that the most sensitive hypertensive patients did not receive this higher dose. Observations made on hypertensive patients during anesthesia, however, when the blood pressure was at a low level, showed them also to be more sensitive to large doses. The reflex slowing of the pulse due to blood pressure rise was less apparent and sometimes completely lacking in hypertensives.

Comment. From these limited observations it would appear that hypertensives are more sensitive to nor-epinephrine than normotensive subjects.

The blood pressure concentration action curves obtained in normals and hypertensives resemble ascending limbs of hyper-

bolae.* The difference in sensitivity to nor-epinephrine between normals and hypertensives is significant, judged both from the curves and the statistical analysis.

It is possible that the increased sensitivity of hypertensives to nor-epinephrine is due

plays an important rôle in the mechanism of essential hypertension. If nor-epinephrine is the “mediator” of essential hypertension, its site of release is confined to the sympathetic nerve endings. The fact that nor-epinephrine infusion causes an increase of

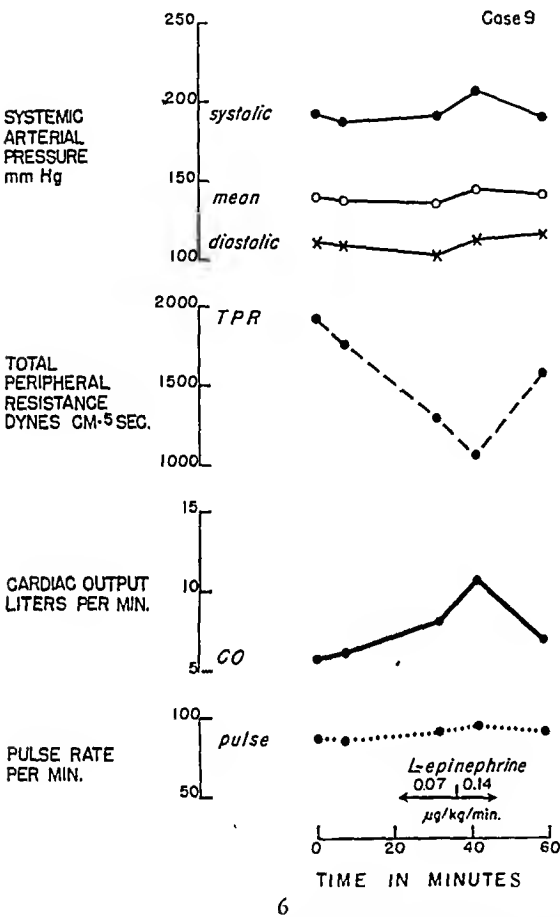
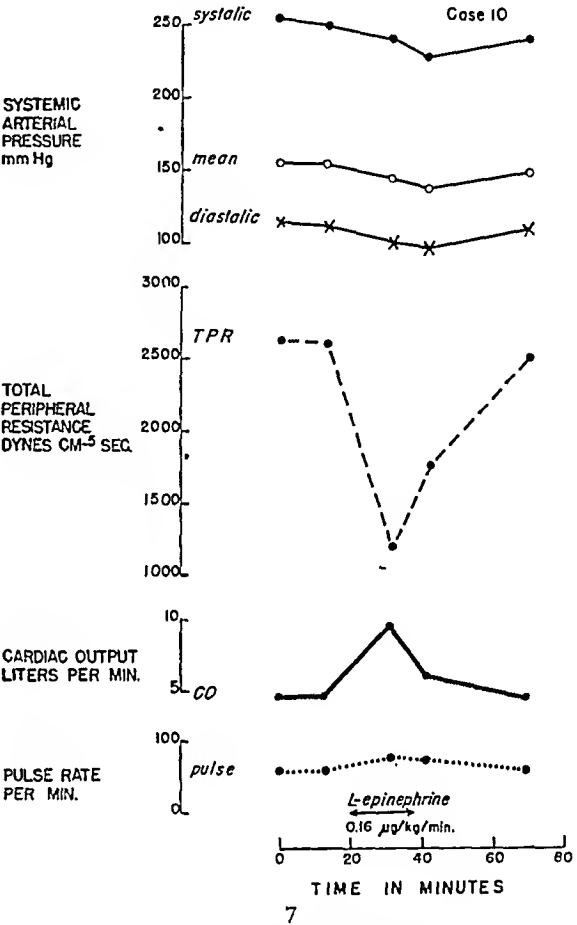


FIG. 6. The hemodynamic changes observed in Case 9 during the infusion of *l*-epinephrine.
FIG. 7. The hemodynamic changes observed in Case 10 during the infusion of *l*-epinephrine.



to the lack of an antagonistic factor, epinephrine, in the peripheral nerve endings. This is analogous to the shift in concentration action curves for a mixture of epinephrine and its antagonist, ergotamine, as compared with the curves for epinephrine alone.¹⁶

COMMENTS

From these experiments it is tempting to develop the hypothesis that nor-epinephrine

* No concentration action curves derived from animal experiments are available for nor-epinephrine but they can be expected to obey the same laws as those for epinephrine or acetylcholine and to give rectangular hyperbolae.^{9,32,41} This is true for excitator and inhibitor actions as well.

pulmonary arterial pressure whereas in uncomplicated essential hypertension the pulmonary pressure values are normal⁶ casts doubt upon the view that nor-epinephrine is present in significant amounts as a circulating agent.

Two possible mechanisms of transmission remain: (1) an increase of sympathetic tone in areas where nor-epinephrine is the mediator, producing vasoconstriction, or (2) an excess of nor-epinephrine due to failure of methylation or lack of methyl donors. The second possibility assumes that normal sympathetic activity is due to the presence of both epinephrine and nor-

epinephrine in varying amounts as suggested by Bacq.³ Thus, essential hypertension might be considered to be a metabolic disease of deficient transmethylation although no definitive evidence is provided by the present study.

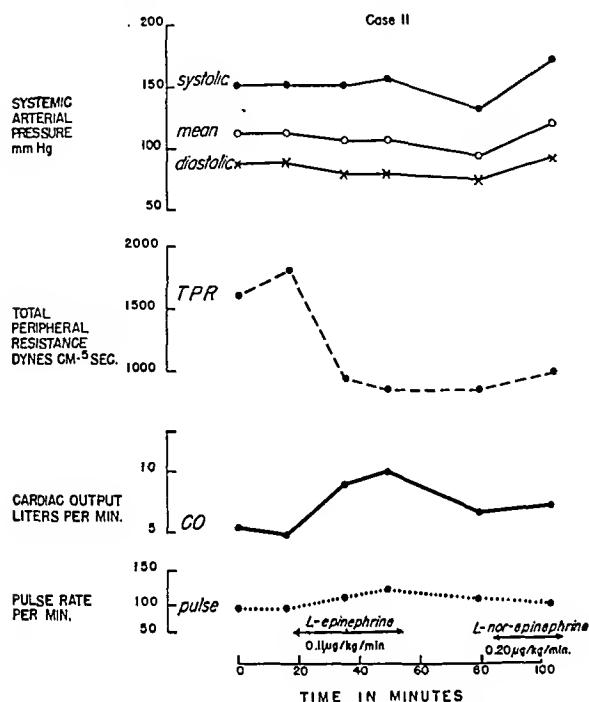


FIG. 8. The hemodynamic changes observed in Case II during the successive infusion of *L*-epinephrine and *L*-nor-epinephrine.

SUMMARY AND CONCLUSIONS

Using the technic of right heart catheterization, eight normotensive and three hypertensive patients were studied during the infusion of varying doses of epinephrine, nor-epinephrine and a mixture of the two substances. Direct measurements made included the cardiac output by the direct Fick method and the simultaneous recording by Hamilton manometers of the systemic and pulmonary arterial pressures. In addition, the systemic blood pressure and pulse rate of twenty normotensive and sixteen hypertensive patients were followed during similar infusions. Epinephrine, in doses sufficient to cause significant hypertension, was found to act as an overall vasodilator as well as a powerful cardiac stimulant. The hemodynamic response of the hypertensive patients to epinephrine differed

from that of the normal subject quantitatively rather than qualitatively. It was characterized both by a marked lowering of the total peripheral resistance to normal levels and frequently by a fall of the systemic arterial pressure. The primary action of nor-epinephrine was intense vasoconstriction. No significant cardiac action was observed in the range of dosage employed. This vasoconstrictor action was completely blocked by the synchronous administration of equal doses of epinephrine. Nor-epinephrine produced a type of hypertension that closely resembled essential hypertension. Patients with essential hypertension showed an increased pressure response to nor-epinephrine as contrasted with normotensive subjects. It is possible that this increased sensitivity is due to the lack of an antagonistic factor, epinephrine, in the peripheral nerve endings. Our findings are compatible with the concept that nor-epinephrine is a sympathetic mediator of overall vasoconstriction and suggest that a disturbed balance between both "sympathetic transmitters" could be concerned in the production of hypertension. The mean pulmonary arterial pressure was increased by the infusion of both substances, but it was impossible to decide from our own data whether this increase was due to back pressure from an elevated left auricular pressure or to vasoconstriction of the pulmonary vascular bed.

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Effect of Tetraethylammonium in Arterial Hypertension*

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IN previous reports we¹⁻³ have described the pharmacologic effects of tetraethylammonium ion (TEA) in normal and hypertensive subjects and in persons with arteriosclerotic vascular disease. Our results on the whole coincide with those obtained by the group at the University of Michigan⁴⁻⁶ except that we found the vasodilator effect of TEA to be inferior to that produced by local nerve and paravertebral block. Similar results have since then been published by others.⁷ In our first paper¹ we suggested that TEA might be of value as a preoperative test in hypertension for the purpose of selecting patients suitable for lumbodorsal sympathectomy. Such studies have also been carried out by others.⁸⁻¹¹

The purpose of the present investigation was to study the effect of a standardized dose of TEA on a larger group of patients with hypertension, divided according to age and height of blood pressure, and to compare the effect of TEA upon blood pressure with the spontaneous variability of blood pressure during rest. We have also studied the influence of TEA on the pressure in the right auricle and ventricle and the pulmonary artery, its effect on cardiac output determined according to the direct Fick principle and its effects on the mean systemic pressure by intra-arterial registration.

MATERIAL AND METHODS

Seventy-one patients with hypertension were studied. Their ages varied between nineteen and

seventy years. All patients were hospitalized and in all of them the following examinations were carried out: Spontaneous variation in blood pressure recorded during standardized serial determinations (twenty-four-hour recordings),¹² eyeground examination and complete examination of the heart and kidneys. The highest systolic pressure varied between 160 and 270 and the highest diastolic pressure between 100 and 170 mm. of mercury.

The test dose consisted of 5 mg. of TEA per Kg. of body weight administered intravenously. This dose was chosen because we³ have noted that a larger dose of TEA may be dangerous in angina pectoris and in hypertension in patients with marked generalized arteriosclerosis, whereas a dose of 5 mg. may be considered safe. In nineteen cases we have compared the effect of a dose of 5 mg. and of 10 mg. of TEA in the same patient.

All patients were in the recumbent position when the test was performed. Before the injection blood pressure and pulse rate were recorded several times until constant levels were obtained and this was repeated every minute after the injection until the blood pressure started to rise again, i.e., for ten to twenty minutes. The lowest pressure and the maximum change in pulse rate registered after the injection were used in the calculation of the effect of TEA.

The technic of heart catheterization and pressure registration has recently been described.¹³

RESULTS

The individual response to a standardized dose of TEA showed great variations even in cases which were clinically similar. No statistically proved difference between vari-

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ous groups of hypertensive patients could therefore be demonstrated. When the material was divided according to age and to height of blood pressure, however, there were some differences. As seen in Table I the mean drop in both systolic and diastolic

TABLE I
EFFECT OF TEA IN HYPERTENSIVE PATIENTS CLASSIFIED
ACCORDING TO BLOOD PRESSURE LEVEL

Blood Pressure before TEA	No. of Cases	Blood Pres- sure before TEA Mean	Effect of 5 mg. of TEA/Kg. of Body Weight Administered Intravenously			
			Drop in Blood Pressure (mm. Hg)		Change in Pulse Rate (beats per min.)	
			Mean	Limits	Mean	Limits
Systolic						
145-195.....	34	173	37	5-75	+17	-12 + 36
>200.....	34	220	56	5-130	+15	-16 + 44
Total.....	68	197	47	+16	
Diastolic						
90-105.....	16	99	13	0-30	+15	0 + 36
110-130.....	33	115	24	0-50	+18	-12 + 36
>135.....	19	140	29	0-60	+13	-16 + 44
Total.....	68	118	23	+16	

pressure was greater in patients with a higher initial pressure elevation than in subjects with a lower elevation. This is in accordance with the results of Lyons et al.¹⁰ They found that the mean decrease in diastolic pressure after administration of TEA increases with increasing initial diastolic elevation. The effect upon the pulse rate was about the same in patients with a great or slight increase in blood pressure. (Table I.)

In Table II the extent of the fall in blood pressure after TEA is compared with the spontaneous pressure variations at rest. The average decrease in pressure after TEA on the whole coincides with the spontaneous variability. In hypertensive patients with a systolic pressure lower than 200 mm. of mercury and a diastolic lower than 110 the lowest pressure obtained after TEA agrees with the lowest spontaneous value. In subjects with a higher elevation in the blood pressure TEA causes a fall in pressure below the lowest spontaneous value. The pulse pressure thus is diminished to a greater

extent in patients with a higher pressure elevation. In spite of this the increase in pulse rate after TEA is about the same for the different groups.

In Table III the patients are arranged according to age. After administration of

TABLE II
COMPARISON BETWEEN THE EFFECT ON BLOOD PRESSURE
OF 5 MG. OF TEA/KG. OF BODY WEIGHT ADMINISTERED
INTRAVENOUSLY AND THE SPONTANEOUS VARIABILITY
OF BLOOD PRESSURE IN SIXTY-EIGHT HYPERTENSIVE
CASES

Blood Pressure before TEA	No. of Cases	Drop after TEA (mm. Hg) Mean	Differ- ence be- tween Highest and Lowest 24-hr. Read- ings Mean	Lowest Pressure after TEA Mean	Lowest Pressure at 24-hr. Reading Mean
Systolic					
145-195..	34	37	50	136	138
>200...	34	56	52	164	180
Total.	68	47	51	150	159
Diastolic					
90-105..	16	13	24	86	84
110-130..	33	24	31	91	94
>135...	19	29	28	111	116
Total.	68	23	29	95	96

TEA the average fall in systolic pressure was least in the youngest group and greatest in the oldest. The reduction in pulse pressure was also most pronounced in the oldest group. The effect upon the pulse rate was the opposite, the youngest patients showed the greatest increase and the oldest the lowest. On the whole, the spontaneous variations in blood pressure were the same for all groups.

The older patients showed the highest initial elevations in blood pressure. In the preceding pages we have shown that the extent of the pressure fall increases with increasing initial elevation. It is therefore possible that the differences in the pressure drop for the various age groups were due to different heights of initial elevation. In order to ascertain if the differences in the decrease in pressure between the various

age groups depended on different heights of initial elevation each of the three groups was divided into two subgroups. (Table III.) The first subgroup (A) includes the patients showing a greater fall in systolic

be demonstrated for the two subgroups. The different effects of TEA in the various age groups therefore cannot be explained by differences in the initial pressure elevation. In the two youngest age groups the

TABLE III
EFFECT OF 5 MG. OF TEA/KG. OF BODY WEIGHT ADMINISTERED INTRAVENOUSLY IN SIXTY-EIGHT HYPERTENSIVE PATIENTS CLASSIFIED ACCORDING TO AGE

	No of Cases	Blood Pressure before TEA (mm. Hg)		Effect of TEA			Highest Pressure at 24-hr. Readings (mm. Hg)		Difference Between Highest and Lowest 24-hr. Readings (mm. Hg)	
				Drop in Blood Pressure (mm. Hg)		Change in Pulse Rate Beats/ min.				
		Systolic	Diastolic	Systolic	Dias- tolic		Systolic	Diastolic	Systolic	Dias- tolic
Group I: younger than 45 yr.	20									
Mean.	176	116	36	23	+24	195	123	47	24
Group II: 45 to 55 yr.	32									
Mean.	202	121	47	24	+18	215	129	40	27
Group III: older than 55 yr.	16									
Mean.	206	115	52	13	+ 9	225	133	48	31

Age groups classified according to systolic drop in blood pressure after TEA*

Group I:											
A.....	8										
Limits.....	..	170-190	100-135	40-85	10-50	+12 +36	160-240	110-140	25-90	5-40	
Mean.....	..	179	115	54	29	+23	194	131	41	21	
B.....	12										
Limits.....	..	150-210	100-140	5-35	0-25	+ 8 +42	170-240	100-160	25-90	5-45	
Mean.....	..	174	117	23	13	+25	196	118	53	26	
Group II:											
A.....	15										
Limits.....	..	140-250	90-160	50-85	15-45	-16 +40	180-270	90-160	10-85	15-40	
Mean.....	..	210	127	65	30	+18	223	129	38	24	
B.....	17										
Limits.....	..	145-235	90-150	20-45	10-30	-12 +44	160-250	100-160	20-75	15-45	
Mean.....	..	196	116	34	19	+18	208	129	42	30	
Group III:											
A.....	7										
Limits.....	..	190-225	110-155	70-130	25-60	- 4 +24	215-270	120-160	35-70	20-50	
Mean.....	..	216	126	87	41	+6	242	143	60	39	
B.....	9										
Limits.....	..	170-240	95-120	5-60	0-30	0 +36	165-270	105-170	25-55	20-30	
Mean.....	..	198	105	35	12	+11	200	127	36	26	

* Subgroups A include those patients in whom the systolic drop after TEA is greater than the average drop and those in group B in whom the systolic drop is less than the average in the various age groups.

pressure than the average, the second sub-group (B) patients showing a smaller decrease. Within each age group no difference in the initial pressure elevation could

mean increase in pulse rate for the corresponding subgroups was the same.

The patients in the oldest age group showing the greatest fall in systolic pressure

and the largest reduction in pulse pressure also showed the least rise in pulse rate. In this group the vascular changes were the most pronounced clinically.

Nineteen of the patients were on different occasions given both a dose of 5 mg. and

tions of TEA in hypertensive subjects. Such fluctuations may contribute to the individual differences in response to various dosages of TEA.

In several patients, especially those with mild hypertension, there was no difference

TABLE IV
EFFECT OF TEA (5 MG./KG. OF BODY WEIGHT) ON BLOOD PRESSURES, CARDIAC OUTPUT AND VASCULAR RESISTANCE IN A YOUNG PATIENT WITH ARTERIAL HYPERTENSION

Case K.P. 21 yr.	Before TEA	After TEA					
		30 sec.	3 min.	9 min.	17 min.	25 min.	50 min.
Blood pressure: brachial artery							
systolic.....	256	217	174	192	210	205	236
diastolic.....	139	120	101	112	121	120	132
mean.....	189	160	129	143	154	153	175
Blood pressure: pulmonary artery							
systolic.....	23	...	13	14	16	16	
diastolic.....	9	...	6	4	6	6	
mean.....	13	...	9	8	10	10	
Blood pressure: right ventricle							
systolic.....	30	37	21	28	
diastolic.....	-0.4	-0.8	-0.4	1.5	
mean.....	9	11	6	8	
Heart rate per min.....	111	136	118	100	107	102	100
A-V oxygen difference, cc./l.....	31	...	42	...	38	37	
Cardiac output, l/min.....	6.98	...	5.38	...	5.94	6.1	
Stroke volume, cc./beat.....	63	...	46	...	55	60	
Peripheral resistance.....	2.162	...	1.920	...	2.070	1.985	
Pulmonary resistance, $\frac{\text{dynes seconds}}{\text{centimeter}^5}$	154	...	134	...	140	112	

10 mg. of TEA per Kg. of body weight. Their ages varied between thirty-three and seventy years. Only the lowest pressure and the maximum change in pulse rate obtained after the two various doses of TEA were used for comparison of the effect in order to eliminate the error involved in different initial levels of pressure and pulse rate. After a dose of 10 mg. the systolic pressure was an average of 22 ± 19.2 mm. of mercury and the diastolic 12 ± 10.8 mm. lower than when a dose of 5 mg. was given. The large mean errors show the great individual differences in the effect of the doses. As shown by Levinson *et al.*¹⁴ there are considerable daily fluctuations in both the magnitude of the depressor response and the blood pressure floor in serial injec-

in effect between the larger and smaller dose. Ten of the patients were younger than fifty years. In these patients the average fall in systolic and diastolic pressure after a dose of 10 mg. was, respectively, 17 mm. of mercury and 10 mm. greater than when 5 mg. was administered. In the nine patients over fifty years of age the corresponding figures were 29 mm. systolic and 14 mm. diastolic. In these patients, in spite of the greater fall in pressure after 10 mg. of TEA, the pulse rate with this dose was on the average nine beats slower than after 5 mg. In the younger patients there was an average rise in the pulse rate of five beats per minute when the dose of TEA was doubled. The differences in the effect of TEA for different age groups of hypertensives thus

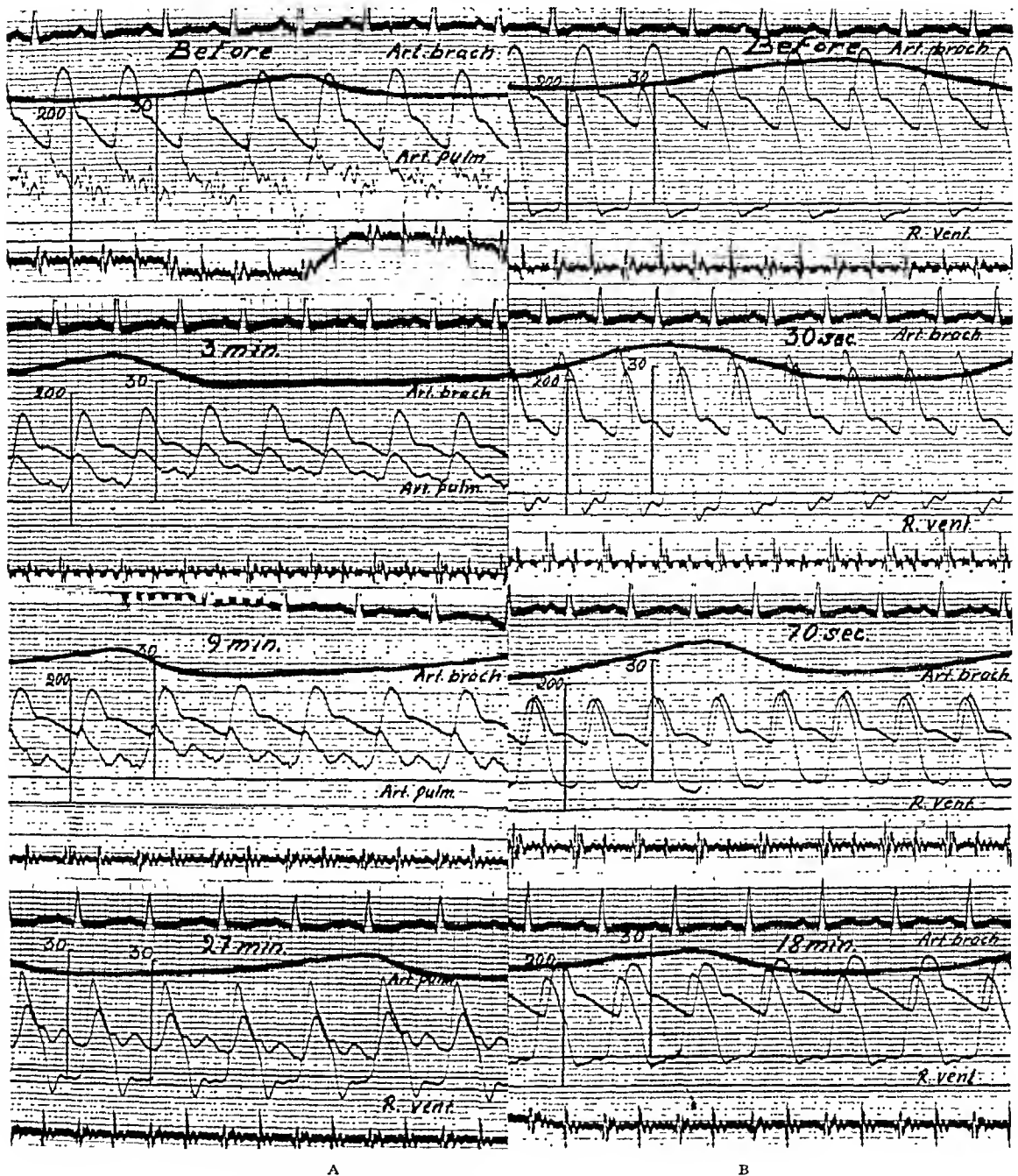


FIG. 1. A and B, the effect of 5 mg. TEA/Kg. of body weight on the blood pressures in the brachial artery, pulmonary artery and right ventricle in a young hypertensive woman. In each section from above down E.C.G. lead II, respiration, brachial arterial pressure, pulmonary arterial or right ventricular pressures and phonocardiogram; standards in mm. Hg. The demonstrated records were taken before, and thirty and seventy seconds, three, nine, eighteen and twenty-seven minutes after the administration of TEA. Note the initial increase in systolic and decrease in diastolic pressure in the right ventricular pressure curve.

became more marked with larger doses. This also demonstrates the risk of giving large doses of TEA to older and arteriosclerotic patients as previously pointed out.³

In three patients with arterial hypertension between twenty-one and forty years of age the influence of TEA on the cardiac

output and the pressure in the lesser circulation was studied. Table IV and Figure 1 show the figures obtained in one case. The results were similar in the two other cases studied. Immediately after the intravenous injection of 5 mg. per Kg. of body weight the systemic blood pressure decreased and the

pulse rate increased. With the increase in pulse rate, there was a slight rise in the systolic pressure in the right ventricle, followed by a decrease. There was a slight decrease in cardiac output three to thirty minutes after the administration of TEA. The end diastolic (filling) pressure in the right ventricle first decreased, then increased to a value higher than the original pressure. The changes in the peripheral vascular resistance were not of the same magnitude as the blood pressure fall due to the changes in cardiac output. The relatively larger fall in blood pressures in the lesser circulation as compared with the systemic circulation indicates a shift of the blood volume toward the peripheral blood vessels.

COMMENTS AND CONCLUSIONS

The decrease in arterial pressure occurring after administration of TEA is caused by ganglionic blockade of the sympathetic nervous system resulting in vasodilatation.^{1,4,5,10} The increase of the pulse rate may be explained either as a compensatory rise in the heart rate in order to counteract the effect of the fall in blood and pulse pressures on the cardiac output or as a direct effect upon the autonomic innervation of the heart.

In younger hypertensive patients without pronounced vascular changes TEA causes a moderate drop in both the systolic and diastolic pressures corresponding to the lowest spontaneous value obtained during rest and sleep. In these patients TEA produces the relatively greatest increase in the pulse rate. Therefore, in this group of patients no greater decrease in the cardiac output should be expected. Our three patients, in whom the influence of TEA upon cardiac output was studied by means of the direct Fick principle, were all under forty years of age and all showed a very slight decrease in the cardiac output. There was a marked lowering of the pressure in the lesser circulation, about one-half of the basic value. This decrease in the pressures was maintained for a considerably longer time than in the peripheral circulation and

probably is not due to the direct influence of TEA on the innervation of the lesser circulation. This innervation plays an uncertain rôle in regulation of the pressure in the lesser circulation.¹⁵ Furthermore, our patients showed an initial increase in the pressure coincident with the rise in pulse rate. The probable explanation of this decrease is that a larger part of the blood volume, because of lessening of the constriction, has been located peripherally. This agrees with the increase in vital capacity observed after administration of TEA to hypertensive subjects.⁹ The vasodilator effect of TEA lasts longer than the decrease in blood pressure. This fact explains why the fall in pressure in the lesser circulation is sustained over a longer period than in the systemic circulation.

Reiser and Ferris¹⁶ have shown that the cold pressor response in hypertensives is eliminated after the administration of TEA. Larsson¹⁷ has demonstrated the essential importance of peripheral vascular tone for the magnitude of the cold pressor response under the influence of TEA. Reiser and Ferris found a delayed cold pressor response in some hypertensives. They refer this delayed effect to a humoral mechanism. Such a suggestion is hardly justified as a delayed cold pressor response could be caused by anxiety. Hammarström¹² has pointed out that centrally acting factors contribute to differences in action of a neurogenic reflex such as the cold pressor response. These factors may also influence the depressor effect of TEA.

In older hypertensive patients with clinical signs of arteriosclerotic changes TEA produces the greatest drop in systolic pressure and relatively the least fall in diastolic pressure. In these cases the decrease in blood pressure after administration of TEA falls below the lowest spontaneous value. The reduction in pulse pressure is greatest in this group and these patients also show the lowest average increase in the pulse rate after the injection of TEA. In some cases there was a slowing of the heart rate. Thus if administration of TEA to a patient

with hypertension produces a noticeable fall in the systolic pressure and a relatively moderate drop in the diastolic pressure simultaneously with a slight increase or decrease in the pulse rate, this is a sign of arteriosclerotic changes. This was strikingly demonstrated by the patient showing the greatest systolic drop after TEA in our series. This man, seventy years of age, had advanced cardioarteriosclerosis and died two months after the TEA test from a rupture of the abdominal aorta. After injection of 5 mg. of TEA per Kg. of body weight the blood pressure fell from 255/155 to 125/90 while the pulse rate varied between 96 and 92 beats per minute.

The degree of reduction in blood pressure after lumbodorsal sympathectomy in hypertension does not run parallel either with the spontaneous variability of the blood pressure or the drop in pressure obtained in preoperative tests with amytal and nitrite.¹² Hammarström¹² found that the lowest blood pressure obtained after amytal agreed in all groups of hypertensives with the lowest spontaneous value. Administration of nitrite to patients with mild hypertension produced a decrease to the lowest spontaneous value whereas in those with more marked vascular changes the blood pressure fell below this level. The effect of a standardized dose of TEA upon the blood pressure thus agrees best in various hypertension groups with the effect obtained after nitrite administration. The various groups of hypertensive patients in Hammarström's series agree well with the groups in this present series, with respect to age, average height of blood pressure and degenerative vascular changes. A comparison of the effect of nitrite and of TEA indicates that in cases with vascular changes TEA produces a larger fall in systolic pressure and a greater reduction in pulse pressure than nitrite.

Conflicting opinions have been expressed regarding the value of TEA as a preoperative test for sympathectomy in hypertension.⁸⁻¹¹ With the exception of Lyons et al.,¹⁰ the different points of view have been based

upon results in small series of patients. The results of Lyons et al.¹⁰ show that poor response of the diastolic pressure to TEA indicates a poor result of sympathectomy. On the other hand, a good response of the diastolic pressure did not guarantee a favorable effect from the operation. Our results show that it is possible even in this latter group to select patients suitable for operation if consideration is taken not only of the fall in diastolic pressure but also of the change in pulse rate and pulse pressure. A marked drop in systolic pressure and a great reduction in pulse pressure with little or no increase in pulse rate after administrations of TEA indicates advanced degenerative changes associated with hypertension. According to clinical experience, sympathectomy is of less value in these cases.

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Effect of the Low Sodium Diet and the Rice Diet on Arterial Blood Pressure*

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INTEREST in the dietary treatment of hypertension has recently been stimulated by the work of Kempner,¹ Grollman,² Perera³ and others.^{4,5} In much of the previous work on the effect of diet on hypertension the control periods were not adequate. Schroeder⁶ reviewed the literature on the low sodium diet in essential hypertension and pointed out the importance of sufficiently long control periods in judging the effects of any therapeutic measure in this disease. This report is based upon our observations of a group of hypertensives who were followed over a prolonged period prior to and after the introduction of dietary therapy. Because the proponents of the rice diet claim specific virtues for that diet, a comparison was made between the rice diet and a diet low in sodium but adequate in protein.

METHODS

Nine patients with essential hypertension, three females and six males ranging in age from thirty-two to fifty-nine, were studied. Two of the nine patients had impairment of renal function but no nitrogen retention. There was no evidence of primary renal disease nor of cardiac failure.

All nine patients were hospitalized throughout the period of study. Each patient was studied in a control period averaging one month directly prior to the institution of dietary therapy. In this period they were on the ward diet containing approximately 2,100 calories and 6 Gm. of sodium chloride. Estimation of arterial blood pressure was made twice daily under the same conditions, urinary output was recorded and frequent determinations of blood and urinary

sodium were made with a flame photometer.* Blood pressure determinations were made by two observers, in the morning with the patient recumbent and in the afternoon with the patient up and about. After the control period the patients were placed on the dietary regimen for not less than four weeks. The low sodium diet provided 1,800 calories, 70 Gm. of protein and 300 mg. of sodium. The rice diet contained 2,000 calories, 20 Gm. of protein and 150 mg. of sodium. While the patients were on this restricted diet, the same observations were made as during the control period but more frequent determinations of urinary sodium were made to assure ourselves that the patients were adhering to the diet. Seven patients were studied on the low sodium diet; of these four received the rice diet in addition. One patient had the rice diet alone and one was dropped from the study when it was found he was not adhering to the diet.

The blood pressure values recorded in the following tables represent the average of the last ten days of measurements during each dietary period. The average of the last ten days of each period was chosen since it was thought this represented the maximum effect of diet. The standard errors of the means of these values is in the order of plus or minus 3. The differences were subjected to analysis by Fisher's *t* test.

RESULTS

In two of the patients, H. H. and R. S., there was a fall in plasma sodium level while on the rice diet but a comparable fall did not occur on the low sodium diet. In

* Sodium determinations were done by Dr. Robert Berliner of the Columbia University Research Service, Goldwater Memorial Hospital.

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patients G. M. and L. N. a significant fall in plasma sodium level occurred while they were on the low sodium diet. (Table I.) In all patients the urinary sodium excretion fell to very low levels on both diets, but the levels on the rice diet were somewhat lower than on the low sodium diet. This was

attributed to the lower sodium content of the rice diet. This fall in urinary sodium generally occurred from the third to the seventh day of dietary restriction.

All of the patients on the restricted diets experienced a weight loss ranging from $4\frac{1}{2}$ to 14 pounds. The weight was regained

TABLE I
DATA ON REGULAR, LOW SODIUM AND RICE DIETS: PLASMA AND URINE SODIUM LEVELS AND AVERAGE ARTERIAL BLOOD PRESSURE READINGS

Case	Diet	Sodium		Blood Pressure		Duration of Period	Weight
		Blood *	Urine †	Systolic	Diastolic		
I H. H.		mEq./L.	mEq. (24 hr.)				
	Regular I	137-142	70-103	218	127	4 wk.	144
	Low sodium	144-136	6-10	217	132	6 wk.	135
	Low sodium + mercurial injections	134-137	360-160 ‡	186	115	2½ wk.	128-134
	Rice diet	136-130	1-4	180	114	5 wk.	146-137
	Rice + salt (6-12 Gm.)		141	204	118	13 days	138
II S. D.	Regular I	139-145	65-103	166	104	5 wk.	166
	Low sodium	143-137	16-19	139	95	6 wk.	160
	Low sodium + mercurial injections	136-139	266-120 ‡	152	100	3½ wk.	155
	Regular II	141	56	163	105	6 wk.	166
	Rice	141-139	1-4	132	86	5½ wk.	158
	Rice + 12 Gm. salt		315	151	94	2 wk.	159
III G. K.	Regular	138	90	240	136	8 wk.	130
	Low sodium	138-131	8-13	224	131	5 wk.	116
	Rice	136	7-8	236	132	4 wk.	129-115
IV R. S.	Regular I	138	80	173	106	4 wk.	131
	Low sodium	138	3-6	164	100	4 wk.	126
	Rice diet	136-132	1-3	164	99	4 wk.	118
V L. N.	Regular I	143	75	205	143	17 days	85
	Low sodium	144-132	3-9	169	125	2 months	79
	Regular II	138	97	191	136	3 wk.	83
VI G. M.	Regular diet	138	57-88	221	142	4 wk.	97
	Low sodium	133-132	12-15	230	145	6 wk.	92
VII E. W.	Regular	135	84-95	184	121	2 wk.	123
	Low sodium	136	3-9	168	110	4 wk.	116
VIII M. W.	Regular	138	68	212	122	3 wk.	133
	Rice	138	6-9	194	112	4 wk.	125

* Figures represent the range of values during each period.

† Figures denote the range of values after five days on the diet.

‡ Figures denote sodium diuresis on the first and second day of mercurial injection.

so quickly after restoration to a regular diet that it probably was caused to a large measure by fluid loss.

CASE REPORTS

CASE I. H. H., a negro man aged fifty, was a known hypertensive of twenty-five years duration. In March, 1947 he suffered a cerebral vascular accident with resultant left hemiparesis. He had complained of headaches for two years.

Upon admission to the hospital the systolic blood pressure was 230 mm. of mercury and the diastolic 135 mm. The fundi revealed Keith-Wagner changes, grade II to III. The heart was slightly enlarged to the left on x-ray examination. There was evidence of left hemiparesis. The maximum specific gravity of the urine was 1.020. He excreted 55 per cent of the phenolsulfonphthalein injected within two hours. The urea clearance was 102 per cent of normal.

The arterial blood pressures and the blood and urinary sodium values are noted in Table 1. During the control period the patient's blood pressure became stabilized at a level of 218 mm. of mercury systolic and 127 mm. diastolic. In this patient the low sodium diet had no effect until ammonium chloride and two injections of mercupurin were given after six weeks of sodium restriction. A marked sodium diuresis was obtained and a persistent, significant fall in both systolic and diastolic pressures occurred. The patient was then placed on a regular diet and after the pressure had become stabilized at about the control levels he was placed on the rice diet for a period of five weeks. The fall in systolic and diastolic pressure was of about the same magnitude as occurred on the low sodium diet after mercurial injection. The decline in blood pressure was not associated with any amelioration of the headaches.

CASE II. S. D., a white man aged fifty-four, had his first cerebral vascular accident in 1943. It was at that time that his hypertension was first discovered. Since then, he has had two further cerebral vascular accidents resulting in right hemiparesis. There was no dyspnea, orthopnea or edema and only occasional headaches. Upon admission to the hospital the systolic pressure was 220 mm. of mercury and the diastolic 120 mm. The fundi showed grade II to III Keith-Wagner changes. The heart was slightly enlarged on x-ray examination. Neurologic examination showed evidence of right

hemiparesis. The maximum specific gravity of the urine was 1.025 and the urea clearance was 125 per cent of normal; 50 per cent of the phenolsulfonphthalein injected was excreted within two hours.

The data on this patient are shown in Table 1. During the control period the patient showed a striking fall in blood pressure. After the pressure had become stabilized at about 166/104 the patient was placed on the low sodium diet for a period of six weeks and the pressure then declined to a level of 139 mm. of mercury systolic and 95 mm. diastolic. This decline was not further augmented by the use of ammonium chloride and mercurial injections. Following the low sodium diet, the patient was placed on the regular diet again for a period of six weeks. After stabilization of the blood pressure had occurred the rice diet was instituted for a period of six weeks and there was a fall of the blood pressure to 132/85. The fall on the rice diet was slightly greater than that achieved on the low sodium diet. The addition to the rice diet of 12 Gm. of salt in enteric-coated tablets over a period of two weeks resulted in a significant rise in blood pressure.

CASE III. G. K., a white man aged fifty-eight, had a cerebral vascular accident in 1940 resulting in left hemiplegia. It was at this time that hypertension was first noted. His past history was essentially negative except for poliomyelitis at the age of eight. Upon admission to the hospital the systolic pressure was 224 mm. of mercury and the diastolic 120 mm. Examination of the fundi revealed grade III Keith-Wagner changes. There was no evidence of cardiac enlargement by x-ray. Neurologic examination revealed the presence of residual left hemiplegia and atrophy of the muscles of the right lower extremity. The maximum specific gravity of the urine was 1.019, 30 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours. The urea clearance was 35 per cent of normal.

The data on this patient are shown in Table 1. After a control period of eight weeks the patient was placed on the low sodium diet. The fall in systolic and diastolic pressure was slight and statistically not significant. A four-week trial on the rice diet did not alter the pressure. There was no change in the electrocardiogram, fundi or size of the heart on either diet.

CASE IV. R. S., a white man aged fifty-nine, had a cerebral vascular accident at the age of

forty-nine, with resultant right hemiparesis and motor aphasia. At that time hypertension was first discovered. The patient had no symptoms referable to hypertension prior to the occurrence of the cerebral vascular accident. Upon admission to the hospital the systolic pressure was 230 mm. of mercury and the diastolic 130 mm. There was a moderate degree of sclerosis of the peripheral vessels. There were no pulsations present in the left external carotid artery. The fundi showed mild arteriosclerotic changes. Right hemiplegia was present. The heart was not enlarged on x-ray examination. In 1940 the left common and internal carotid arteries were excised. Maximum specific gravity of the urine was 1.031; 50 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; urea clearance was 77 per cent of normal.

The data in Table 1 reveal a minimal fall in systolic and diastolic pressures after four weeks on the low sodium and after a similar period on the rice diet.

CASE V. L. N., a colored female aged fifty-one with tabes dorsalis for fifteen years, was admitted to this hospital in March, 1944 for custodial care. There was no history of hypertension prior to admission. Upon admission the systolic blood pressure was 180 mm. of mercury and the diastolic 120 mm. Examination of the fundi showed moderate hypertensive changes. The heart was normal in size and shape by x-ray examination. The neurologic examination confirmed the diagnosis of tabes dorsalis and there were Charcot joints in both hips. The maximum specific gravity of the urine was 1.020; 30 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; the urea clearance was 45 per cent of normal; the blood urea nitrogen was 18 mg. per cent. The urine contained no albumin; occasional white blood cells were seen upon microscopic examination. Retrograde pyelography revealed the right kidney to be rotated and the left kidney posed with the pelvis slightly dilated.

The patient had been hospitalized at this hospital for over three years prior to this study and all blood pressure determinations were markedly elevated. The patient was observed for seventeen days and when her blood pressure was stabilized she was placed on the low sodium diet. She was given a low sodium diet for eight weeks. A significant decline in blood pressure occurred. (Table 1.) After cessation of the low sodium diet the blood pressure, which was

followed for three additional weeks, began to approach the levels of the control period.

CASE VI. G. M., a white female aged thirty-two, had a history of headaches for over twenty years. Headaches were occipital and occurred in the morning upon arising. In 1943 at the age of twenty-eight she sought medical advice at which time hypertension was first discovered. In May, 1947 because of severe epistaxis the patient was admitted to another hospital where the diagnosis of malignant hypertension was made. In June, 1947 she underwent bilateral sympathectomy with diminution in frequency but not in the severity of the headaches. She was transferred to Goldwater Memorial Hospital for further care in August, 1947. Upon admission to this hospital the systolic pressure was 200 mm. of mercury and the diastolic was 140 mm. Examination of the fundi revealed grade IV Keith-Wagner changes. There was a harsh, apical, systolic murmur transmitted to the base and axilla. Fluoroscopic examination showed slight enlargement of the left ventricle. Well healed operative scars were noted in both flanks. The maximum specific gravity of the urine was 1.014; 25 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; urea clearance was 24 per cent of normal. The blood urea nitrogen was 18 mg. per cent.

The data in Table 1 indicate that after a period of six weeks on the low sodium diet there was no significant change in blood pressure. The patient had no relief from her headaches and there were no changes in the heart size or electrocardiogram. The patient had a progressive downhill course and died of a cerebral hemorrhage seven months after admission.

CASE VII. E. W., a colored male aged thirty-eight had complained of headaches of six months' duration which were associated with nausea but no vomiting. Hypertension was discovered two months prior to admission. Because of the increasing severity of his headaches, the patient was admitted to the hospital. His past history was non-contributory. Upon admission the systolic blood pressure was 180 mm. of mercury and the diastolic 120 mm. Examination of the fundi revealed moderately severe hypertensive changes. There was no cardiac enlargement demonstrable on physical or x-ray examination. The maximum specific gravity of the urine was 1.020; 45 per cent of the phenolsulfonphthalein injected was excreted at the end

of two hours; the urea clearance was 70 per cent of normal.

Because the patient was gainfully employed, control observations were limited to two weeks before he was placed on the low sodium diet. After a month on the restricted diet there was a statistically significant fall in systolic and diastolic pressures to 168/110. (Table 1.) These changes were not of great magnitude. There was no improvement in the patient's symptoms of headache and nausea.

CASE VIII. M. W., a white widow aged forty-two, was admitted to this hospital for treatment of hypertension of five years' duration. Her only complaint was easy fatigability and malaise. There was no history of scarlet fever, nephritis or hypertension associated with pregnancy. Upon admission the systolic blood pressure was 250 mm. of mercury and the diastolic 150 mm. Examination of the fundi showed moderately severe hypertensive changes. There was no enlargement of the heart on physical or x-ray examination. The electrocardiogram was abnormal with depressed S-T segments in leads 1 and V₅ with diphasic T₁ and inverted TV₅; there was left deviation of the electrical axis. Maximum specific gravity of the urine was 1.028; 40 per cent of the phenolsulfonphthalein injected was excreted at the end of two hours; urea clearance was 78 per cent of normal. Blood urea nitrogen was 17 mg. per cent on admission. A retrograde pyelogram showed moderate dilatation of the right renal pelvis.

With rest in the hospital, there was a definite fall in blood pressure and after a three week control period the arterial pressure became stabilized at a lower level. The patient was placed on the rice diet for a period of four weeks and a significant decline in blood pressure occurred as noted in Table 1. No change in heart size was noted. Upon discharge from the hospital after conclusion of the diet therapy the patient was somewhat improved symptomatically.

COMMENT

The low sodium diet, although monotonous, seemed to be better tolerated than the rice diet. There were no symptoms of salt deprivation in any of the patients despite the fact that some of the patients were on the diet during the hot summer months. As has been previously reported¹ there was a

striking fall in blood urea nitrogen and cholesterol in the four patients on the rice diet.

A summary of our observations is charted in Table II. Of the seven patients on the low sodium diet there was no statistically signifi-

TABLE II
SUMMARY OF OBSERVATIONS

Patient	Systolic			Diastolic		
	Con- trol	Low So- dium	Rice	Con- trol	Low So- dium	Rice
	70 mEq. Na	13 mEq. Na	7 mEq. Na			
H. H.	218	186*	180	127	116*	114
S. D.	166	139	132	104	95	86
G. K.	240	224	236	136	131	132
R. S.	173	164	164	106	100	99
L. N.	205	169	...	143	124	
G. M.	221	230	...	142	145	
E. W.	184	168	...	121	109	
M. W.	212	...	194	122	...	112

* After six weeks of salt restriction the patient was given two injections of mercupurin.

cant fall in blood pressure in three (G. K., R. S. and G. M.). In the remaining four (H. H., S. D., L. N. and E. W.) there was a significant fall in systolic and diastolic pressures. However, in one of these (H. H.) the drop in pressure occurred only after salt deprivation for a six-week period was augmented by an injection of 1 cc. of mercupurin on two successive days. Of the five patients treated with the rice diet, three (H. H., S. D. and M. W.) experienced a significant fall in blood pressure. It is of interest that in the two patients (G. K. and R. S.) who did not respond to the rice diet there was also no drop in blood pressure while on the low sodium diet. In the two patients who experienced a fall in blood pressure on both diets (H. H. and S. D.) the fall was somewhat greater on the rice diet. In the entire series there was only one patient (S. D.) who had a fall in systolic and diastolic pressure to levels below 140/95 mm. of mercury on dietary treatment. In

this patient the systolic and diastolic pressures were only slightly elevated during the control period. Of the three patients (G. K., R. S. and G. M.) in whom there was no fall in arterial blood pressure while on salt deprivation diets, two (G. M. and G. K.) had marked impairment of renal function.

In the three patients who complained of headache there was no relief of symptoms although there was a fall in blood pressure in two of them (H. H. and E. W.). There were no significant changes in the electrocardiograms during the dietary therapy.

SUMMARY

1. Nine patients with hypertension were treated by diet. Seven received a low sodium diet adequate in protein; four received the rice diet in addition to this; one had the rice diet alone and in one patient observations were discontinued because he did not adhere to the diet.

2. Four of seven on the low sodium diet experienced a statistically significant fall in blood pressure; in three there was no change. Of five patients on the rice diet three showed statistically significant falls in both systolic and diastolic pressures but only one to a normal value.

3. The effect of the rice diet was only slightly greater than that of the low sodium diet.

4. Although there was a fall in blood pressure in five of the patients studied, there was no relief of symptoms. Although the number of patients studied is small it is believed these changes were not of sufficient magnitude to warrant the routine use of this type of therapy in the management of essential hypertension.

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Electrocardiographic Manifestations of Potassium Intoxication*

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P.V.I.

THE electrocardiographic manifestations of potassium intoxication have been described in the literature, both in experimental animals and in man. Winkler, Hoff and Smith¹ in 1935 correlated the electrocardiographic changes with the level of the serum potassium in dogs. Chamberlain, Scudder and Zwemer² in 1939 and Crisman, Crisman, Calabresi and Darrow in 1943³ made similar studies in cats poisoned with potassium salts given intravenously. Keith, King and Osterberg,⁴ Keith and Osterberg,⁵ Keith, Burchall and Baggenstoss,⁶ Finch and Marchand,⁷ Marchand and Finch,⁸ Finch, Sawyer and Flynn,⁹ Govan and Weiseth¹⁰ and Martin and Wertman¹¹ have correlated the electrocardiographic findings with the level of serum potassium in human subjects who have developed potassium intoxication either spontaneously or following administration of potassium salts.

It has been found that there is first an increase in amplitude of the T waves as the serum potassium rises, then a decrease in amplitude of the R waves with an increase in amplitude of the S waves. As the serum potassium reaches a level of about 10 mEq./L. there is disappearance of the P waves and progressive depression of the RS-T segments with widening of the QRS complexes so that a smooth biphasic curve of the QRS-T appears. With the appearance of intraventricular block, the heart rate falls progressively until there is cardiac arrest in diastole. Other types of abnormalities have been described. Stewart and Smith¹² de-

scribed changes in the T waves and RS-T segments similar to those usually attributed to myocardial damage and changes in rhythm such as incomplete heart block, complete auriculoventricular dissociation and irregularity of the ventricle simulating ventricular fibrillation, in addition to auricular standstill.

Potassium salts have been used therapeutically in the following manner: as diuretics in the treatment of heart failure, in the treatment of cardiac irregularities and of cardiovascular syphilis, as an expectorant, as an alkalinizing agent and in the electrolyte replacement therapy of infantile diarrhea. Smillie¹³ in 1915 was the first to indicate the possible toxic action of potassium salts by mouth in patients with renal disease. His patient recovered. Stewart and Smith¹² emphasized this danger further since one of the patients in the cases reported by them died of cardiac arrest following use of potassium chloride as a diuretic. In none of these reports, however, were potassium levels recorded. The two patients of Finch and Marchand,⁷ whose cases were reported in 1943, had both received potassium salts as a diuretic and both died of cardiac arrest; the serum potassium was elevated.

On the other hand, the earlier studies of Keith and Binger,¹⁴ of Winkler, Hoff and Smith¹⁵ and the more recent studies of Keith and his co-workers^{4,5,16-18} leave the impression that administration of potassium is without danger even in severe renal disease unless there is oliguria or anuria with a blood urea nitrogen retention of 100 mg.

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per cent or more. The toxicity of potassium salts in patients with Addison's disease in which a spontaneous hyperkalemia and decreased renal excretion of potassium is known to occur will not be discussed further. In 1944 Ohnsted and Wolfson¹⁹ recommended use of potassium bicarbonate as an alkalinizing agent in patients with cardiac decompensation who required sulfonamide therapy. They gave potassium bicarbonate 8.0 Gm. as the initial dose and 2.0 Gm. every two hours. They encountered no toxic effects in a series of nine cases. They were careful, however, to exclude those with severe renal disease and with Addison's disease from the patients so treated.

In recent months we have encountered two instances of auricular standstill and widespread intraventricular block associated with marked rises in serum potassium. In one, a man with cardiac failure, potassium bicarbonate was given as an adjunct to sulfonamide therapy. He showed evidence of mild renal insufficiency with a blood urea nitrogen retention of only 31 mg. per cent. In the other case, a boy of three and one-half years, the toxic effects occurred spontaneously in the course of the nephrotic stage of subacute glomerulonephritis. Data relating to these two cases form the basis of this paper.

CASE REPORTS

CASE 1.* M. S., No. 400459, an acutely ill male aged seventy-two, was admitted to the hospital December 13, 1947. He had been in excellent health until approximately eight months before admission when he had a three-day illness and was said to have had bronchopneumonia. He had a similar episode one month before admission. One week before admission he developed a cough and watery diarrhea. His temperature rose to 39.7°C. and he became confused.

Upon physical examination his temperature was 39.2°C., the pulse 104, respirations 40/min. and the blood pressure 96/56 mm. Hg. He was emaciated and coughed frequently. There

was cyanosis. There was dullness at the left base anteriorly and posteriorly and fine râles were heard diffusely over both lung fields. The liver was palpable 7 cm. below the costal margin.

The blood Wassermann was negative, the hemoglobin 11.9 Gm., red blood cells 4.2 million and white blood cells 14.7 thousand. The urine showed 1 plus albumin, occasional white cells and occasional hyaline, granular and cellular casts. The blood urea nitrogen was 31 mg. per cent and the blood proteins were normal. Cultures of the blood and urine were negative. X-ray of the chest showed marked pulmonary congestion with possible small patches of bronchopneumonia widely disseminated throughout both lung fields.

He was placed in an oxygen tent, given penicillin and digitalized. He improved on this regimen. The electrocardiogram (Fig. 1A) showed changes in the T waves and RS-T segments compatible with coronary artery disease and digitalis effect. In order to evaluate the occurrence of diarrhea proctoscopy was done; no abnormalities were revealed. X-ray examination of the large bowel following a barium enema showed diverticulitis of the sigmoid colon.

On December 30, 1947, he had a recurrence of fever and was found to have dullness and coarse rhonchi at the base of the left lung with an increase in diarrhea. Sulfadiazine was given but its use was discontinued three days later because of crystalluria. In order to alkalinize the urine potassium bicarbonate 4 Gm. was given three times a day. It was thought inadvisable to give sodium bicarbonate because of the heart failure. Two days later, after a total of potassium bicarbonate 20 Gm. in a period of forty-eight hours, the pulse was 42/min. when taken on the four-hour schedule. The rhythm was totally irregular. The blood pressure was 80/48 mm. Hg and the respirations 40/min. The extremities were cold and clammy. The patient, however, offered no complaints. An electrocardiogram was taken at once. It showed auricular standstill with the pacemaker arising irregularly from a focus in the right ventricle. The QRS conduction time was 0.15 seconds. (Fig. 1B.) The serum potassium level taken at the time the electrocardiogram was taken was 10.3 mEq./L. and the serum sodium 128 mEq./L.

The potassium bicarbonate was discontinued. The next day the blood pressure was 118/60 mm. Hg and the pulse was regular with a rate of

* We are indebted to Dr. Herbert Koten for permission to report this case.

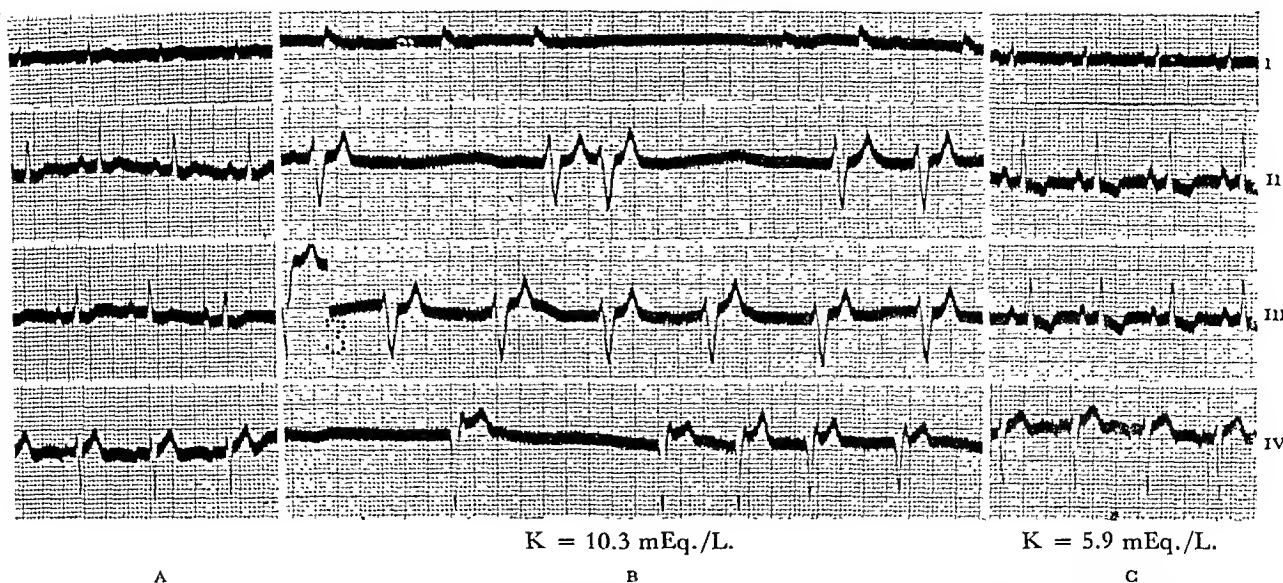


FIG. 1. In this figure are reproduced electrocardiograms of patient M. S. (Case No. 1, Hist. No. 400459), derived from the three standard leads and chest lead IV F. In this and the following figure the standardization in all leads was such that 1 millivolt produced 1 cm. deflection of the string. Divisions of the ordinates equal 10^{-4} volt. Divisions of the abscissae equal 0.04 second. In this and the following figure K = serum potassium in milliequivalents. The electrocardiograms shown in Figure 1A were taken January 2, 1948, before the administration of potassium. The electrocardiograms shown in Figure 1B were taken January 5, 1948, after the administration of potassium bicarbonate, 20 Gm. in forty-eight hours. The electrocardiograms shown in Figure 1C were taken January 6, 1948, eighteen hours after the administration of potassium had been discontinued.

90/min. He was free of complaints. The electrocardiogram now showed that marked changes had taken place in comparison with the previous record and that the form of the electrocardiogram had returned to its previous configuration. (Fig. 1c.) The serum potassium had fallen to a level of 5.9 mEq./L., normal values being considered to fall within the range of 3.9 to 5 mEq./L. The serum sodium was unchanged. The remainder of the patient's course in the hospital was uneventful and he was discharged improved on January 17, 1948.

Case II.* M. K., No. 492328, a male aged three and one-half years, was first admitted to the hospital October 29, 1947, because of swelling of the legs and he was discharged December 10, 1947. His birth and early development were normal. At the age of one and one-half years his management became difficult because of a feeding problem. At two years he was found to be anemic. He had suffered frequent respiratory infections, several of which had been treated with either penicillin or a sulfonamide. In April, 1947 his tonsils and adenoids were removed in the hope of reducing these infections.

* We wish to thank Dr. S. Z. Levine and Dr. H. Barnett for permission to report these data of this patient.

He had had no known contagious disease. Two days before admission he awoke with swollen eyelids and on the morning of admission his legs were swollen. He had had frequency of urination, with nocturia four to five times a night for several days.

Upon physical examination the significant findings were as follows: the blood pressure was 108/60 mm. Hg. The pulse rate was 110/min. and there was moderate edema of the eyelids and feet. The results of serologic tests were negative and the blood count was within normal limits. The urine specific gravity ranged from 1.010 to 1.030. The albumin in the urine ranged from 3 to 4 plus; there were a few red cells and white cells, and hyaline and granular casts upon microscopic examination. The blood urea nitrogen varied from 10 to 57 mg. per cent; the CO_2 combining power was 56.3 vol. per cent; the serum chlorides (as NaCl) were 105 mEq./L. The serum albumin was 2.0 Gm. per cent and serum globulin 2.4 Gm. per cent. The sodium was 141 mEq./L. The sedimentation rate was 16.5 mm. in one hour. The renal function tests showed a phenolsulphonphthalein excretion of 30 per cent in five hours and a urea clearance of 19.3 per cent. Blood cultures were negative, and nose and throat cultures grew no hemolytic

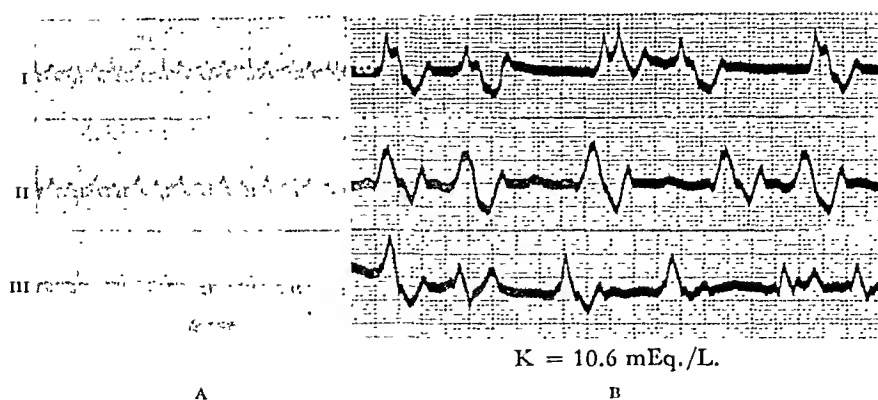


FIG. 2. In this figure are reproduced electrocardiograms of patient M. K. (Case No. 2, Hist. No. 492328) derived from the three standard leads. The electrocardiograms shown in Figure 2A were taken December 1, 1947, during the first admission to the hospital before the development of potassium intoxication. The electrocardiograms shown in Figure 2B were taken January 10, 1948, during the second admission to the hospital showing evidence of potassium intoxication.

streptococci. The electrocardiogram was normal. (Fig. 2A.)

While in the hospital, he developed an upper respiratory infection upon two occasions, during each of which the edema increased. He was treated with penicillin in addition to the basic regimen of a high-protein, low-salt diet, and on each occasion as the infection subsided he had a good diuresis. He was discharged after six weeks in the hospital with a diagnosis of subacute glomerulonephritis with nephrosis.

He was re-admitted to the hospital on January 10, 1948, having contracted a respiratory infection several days before. In association with this he had gained weight. The blood pressure was 90 mm. Hg systolic level, but the diastolic could not be obtained; the pulse rate was 114/min. He appeared acutely ill. The respirations were 24/min. There was moderate ascites and anasarca. The urine contained 4 plus albumin, 1 to 2 white cells per high power field and many granular casts. The white blood cell count was 35.1 thousand, the blood urea nitrogen was 44.5 mg. per cent, calcium 11.3 mg. per cent, phosphorus 8.6 mg. per cent, serum chlorides (as NaCl) 93.5 mEq. L., sodium 120.1 mEq., potassium 10.6 mEq./L. and proteins 3.8 Gm. per cent.

He was placed in an oxygen tent. Shortly after admission the pulse was found to be 68/min. Auscultation of the heart revealed a slow irregular rhythm, each beat being associated with three distinct sounds suggesting a gallop rhythm. An electrocardiogram showed auricular standstill with the pacemaker arising irregularly from a focus in the right ventricle

giving rise to coupled rhythm in all leads. (Fig. 2B.) The rate was 70/min. The QRS time varied between 0.20 and 0.26 seconds. He was given salt and salty broth by mouth with temporary improvement. The rhythm became regular, and he was allowed out of the oxygen tent. The next day he became restless, the pulse could not be obtained and he expired. Post-mortem examination revealed no pathologic changes in the heart and the kidneys showed minimal evidence of renal disease.

COMMENT

The importance of the rôle of potassium in cardiac physiology has been well substantiated by experimental and clinical data. Except for the studies of Stewart and Smith¹² and of Thomson²⁰ in the past decade and the recent report of Tarail,²¹ it has been the consensus that potassium intoxication can assume dangerous proportions only in the presence of severe renal disease. The two cases presented herein indicate that this is not always the case.

The first patient had only slight nitrogen retention and no oliguria, but with doses of potassium which were not large, namely, 4 Gm. of the bicarbonate three times a day for two days to a total dose of 20 Gm., he developed potassium intoxication. He was given no therapy to counteract the potassium effects because it was thought that since he had no evidence of severe renal disease and was without evidence of cardiac

failure at this time the kidneys would excrete the excess potassium if the salt was discontinued. This proved to be the case as with excretion of the drug normal cardiac mechanism was restored.

At this point it is of interest to note that of the cases reported by Stewart and Smith¹² in 1941 Case v, on a dose of potassium chloride of 8 Gm. a day and with a blood urea nitrogen retention of only 60 mg. per cent, developed fatal potassium intoxication as shown by auricular standstill and intraventricular block in the electrocardiogram, with death due to cardiac arrest. The level of blood potassium was not estimated in this patient.

The second patient had subacute glomerulonephritis in a nephrotic stage, with oliguria. He had been on a low-salt diet for many months, such that at the time of his last admission his serum chlorides were 93.3 mEq./L. and his sodium was 120 mEq./L. The potassium was 10.6 mEq./L. at the time that the electrocardiogram showed auricular standstill and intraventricular block. He was treated with salt by mouth with temporary return of regular rhythm but, in the absence of further electrocardiograms and further electrolyte studies, the exact mechanism of his subsequent exitus is not certain. It seems likely that he died of potassium intoxication, particularly as the autopsy findings gave no clue as to the cause of death. A review of the literature reveals that this represents the first reported case of death from potassium intoxication in the nephrotic stage of subacute glomerulonephritis with only moderate nitrogen retention.

The electrocardiographic manifestations of potassium intoxication in these two cases are unmistakable, and it was the electrocardiogram in each case which pointed the way to the correct diagnosis. Auricular standstill is a rare occurrence, which has been pointed out by Rosenbaum and Levine,²² and has usually been attributed to the toxic effect of either digitalis or quinidine. It is difficult to be certain of the diagnosis of auricular standstill when the

ventricular complexes assume a regular and supraventricular form as a nodal rhythm with P waves buried in the QRS complexes may have the identical pattern. However, when no P waves are seen in the electrocardiogram and there is intraventricular block with an irregular rhythm it is apparent that auricular standstill is present. Thus, potassium intoxication should be considered as a possible cause in addition to the other known causes such as digitalis and quinidine intoxication. If potassium is implicated in the presence of these two electrocardiographic abnormalities, it is likely that the serum potassium level will be about 10 mEq./L. Indeed, in both of these cases the electrocardiographic diagnosis of potassium intoxication was made and this was the basis for the potassium analyses.

Experience with the treatment of this condition has been limited as the number of cases is small. The natural history of the phenomenon is such that either sudden death from cardiac arrest will occur in a few hours or recovery will ensue, the outcome depending upon the nature of the underlying renal defect. The problem, therefore, is to recognize the condition promptly and to prevent cardiac arrest by prompt and appropriate treatment. Potassium salts should, of course, be discontinued if these are being given, and this may be sufficient.

In the treatment of auricular standstill with ventricular rhythm calcium ions have been used by Stewart and Smith,¹² by Finch, Sawyer and Flynn⁹ and by Govan and Darrow^{10,23} because of their known property of increasing the irritability of cardiac muscle. In the case reported by Stewart and Smith¹² calcium gave a transient increase in cardiac rate but was ineffective in preventing eventual cardiac arrest.

After observing the transient effect of calcium ions Finch, Sawyer and Flynn⁹ were able to correct temporarily the potassium intoxication of patients in the terminal stages of renal disease by use of 3 per cent sodium chloride intravenously. The effect was prompt and dramatic. In one case they

injected 410 cc. of salt solution in thirty-five minutes with return of regular rhythm five minutes later.

In studies relating to the rôle of potassium in the body economy it has been shown that the deposition of glycogen is accompanied by a transfer of potassium from the extracellular phase to the intracellular phase. This was reported by Fenn²⁴ in rats and by Martin and Wertman²⁵ in patients with diabetic acidosis treated with insulin. Moreover, Gass, Cherkasky and Savitsky²⁶ induced attacks of paralysis in patients with familial periodic palsy by administering glucose intravenously. It is recalled that attacks of paralysis in this disease are accompanied by a low level of potassium in the blood. This effect of glucose was turned to advantage by Govan and Darrow²³ who successfully treated potassium intoxication in an infant with diarrhea by use of hypertonic glucose intravenously to promote glycogen deposition; reduction of the level of serum potassium resulted from this measure. They used calcium gluconate simultaneously but, in view of the experience just cited, it seems unlikely that it was of major importance in the therapeutic effect which followed. Their patient had a serum potassium of 12.3 mEq./L., this is probably the highest level reported in man with recovery.

It is paradoxical that the heart failure which may arise secondary to potassium intoxication should be treated by means of intravenous glucose and saline. These measures may, however, be life-saving. In the light of these considerations it is interesting to review the data of Case II, in which post-mortem study revealed evidence of only minimal renal disease. More vigorous therapy in the form of intravenous glucose and saline might have overcome the potassium intoxication in this patient, thereby controlling what might have been a transient episode in an otherwise chronic illness.

The danger of potassium administration, even in the presence of mild renal disease, is emphasized. It is apparent that potassium salts administered for any reason should be

used with extreme caution if there is any possibility of underlying renal disease. This is particularly pertinent in view of the current use of the new salt substitutes containing potassium which have been advocated for cardiac patients. Some of these preparations contain 35 per cent potassium²⁷ with instructions that they may be used in the same quantity as ordinary table salt and without warning as to possible toxic effects. Use of 5 to 10 Gm. of these salt substitutes per day would entail the ingestion of 2 to 4 Gm. of potassium a day. This, even with mild renal disease, may be sufficient to cause potassium intoxication.

SUMMARY

Two cases of potassium intoxication have been presented in which auricular standstill and widespread intraventricular block appeared in the electrocardiograms at a time when the serum potassium had risen to a level of 10 mEq./L. or higher. One occurred following administration of therapeutic amounts of potassium bicarbonate in the presence of only slight urea nitrogen retention. The other occurred spontaneously in the course of the nephrotic stage of subacute glomerulonephritis.

It appears that physiologic saline solution and hypertonic glucose should promptly be administered intravenously in treatment of the cardiac manifestations of potassium intoxication.

The electrocardiographic manifestations of potassium intoxication are reviewed and the danger of administering potassium salts, even in the presence of only mild renal disease, is emphasized.

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Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances*

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ELECTROCARDIOGRAPHIC disturbances have been related directly to abnormalities in the concentration of serum potassium.¹⁻¹⁰ Abnormal reduction in the concentration of serum potassium has been associated with depression of the S-T segment and the T wave, and with increase in the P-R and Q-T intervals. These abnormalities have been said to disappear as the concentration of serum potassium increases.⁴⁻⁸ Abnormal elevation of the concentration of serum potassium has been associated with peaked T waves, prolonged intraventricular and atrioventricular conduction, disappearance of the P wave and depression and obliteration of the S-T segment.^{1-3, 9, 10}

The purpose of this study is to determine in man the relationship between abnormalities in the concentration of serum potassium and electrocardiographic findings. This analysis is based on a survey of the concentrations of serum potassium and of concomitant electrocardiograms in patients suspected of abnormalities in the metabolism and excretion of potassium. One group of patients had low concentrations of serum potassium and cellular depletion of the ion. Another had elevated concentrations as the result of inadequate excretion of the ion. Detailed chemical and metabolic data pertaining to these patients are reported elsewhere.^{11, 12}

EXPERIMENTAL PROCEDURE AND METHODS

Electrocardiograms and specimens of blood for chemical analysis were taken from nineteen patients who had normal renal function and possible deficits of potassium. Low concentrations of serum potassium were observed in four of the patients before treatment with potassium. Significant quantities were retained in the cellular phase when potassium was administered.¹¹ The chemical and electrocardiographic findings in these four patients will be presented. All four were sustained almost entirely on parenteral fluids and were losing abnormal quantities of gastrointestinal fluid.

Seventy electrocardiograms and simultaneous chemical studies were carried out in nineteen cases of renal insufficiency. These patients were part of a group of fifty-one consecutive patients in whom the concentration of blood non-protein nitrogen was found to be greater than 100 mg. per cent. The metabolism and excretion of potassium in these patients will be discussed elsewhere.¹²

Electrocardiograms were usually taken with a conventional amplifier type instrument with photographic recording; occasionally a direct writing instrument was used.† All tracings were taken and mounted by the same observer and were standardized to a deflection of 1 cm. per millivolt.

The chemical methods have been reported previously from this laboratory;^{11, 12} diagnoses and certain clinical details are appended to the illustrations and to Table 1.

† "Visocardicte," Sanborn Company.

* From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. This work was done during the tenure of a Life Insurance Medical Research Fellowship.

TABLE I
RESULTS OF SIMULTANEOUS CHEMICAL AND ELECTROCARDIOGRAPHIC STUDIES IN NINETEEN PATIENTS WITH RENAL INSUFFICIENCY

Patient	Diagnosis	Outcome	Preceding 24-hour Urine Vol. (cc.)	Highest Serum K (mEq./L.)	Time before Death (Hr.)	Elevated K Effect (E.C.G.)	Blood NPN (mg. %)	Serum						Hypertension	Pericarditis	Digitalis	Coronary Disease	Anemia
								CO ₂ (mEq./L.)	Cl (mEq./L.)	Na (mEq./L.)	Ca (mg. %)	P (mg. %)	Prot. (Gm. %)					
R. S.*	Carcinomatous ureteral obstruction	D	0	8.1	3	+	245	91.2	127.0	0	0	0	0	+
P. DeB.*	Acute glomerulonephritis	D	0	8.1	0	+	151	13.1	85.8	128.3	9.6	+	0	+	0	+
P. M.*	Lower nephron nephrosis	D	110	8.3	6	+	201	86.2	121.9	6.2	8.7	5.21	+	0	0	+	0
L. T.*	Pyelonephritis	D	95	6.9†	12	0	185	11.0	136.3	+	0	+	0	+
J. P.	Nephrosclerosis	D	0	7.5	15	+	255	91.9	+	0	+	0	+
F. S.	Nephrosclerosis	D	inc.	4.3	>24	0	88	24.3	93.4	131.0	+	0	+	0	+
C. K.	Intercap. glomerulosclerosis	D	740	5.8	<24	0	204	14.2	93.7	134.9	5.2	13.6	4.90	+	0	+	0	+
A. M.	Nephrosclerosis	D	100	5.7	20	0	245	10.5	94.1	131.4	+	0	+	0	+
W. S.*	Nephrosclerosis	D	986	6.0	<24	0	311	+	+	+	+	+
W. M.	Lower nephron nephrosis	R	210	6.4	0	172	17.3	84.3	133.0	9.2	7.1	6.30	+	0	+	0	+
A. G.*	Polycystic kidneys	D	inc.	6.2	13	0	205	116.3	+	0	+	0	+
O. T.*	Nephrosclerosis	D	300	4.0	>24	0	119	16.9	102.2	137.9	+	0	+	0	+
A. M.*	Pyelonephritis	D	1500	5.0	>24	0	250	7.1	11.1	4.70	+	0	+	0	+
S. M.	Pyelonephritis	R	3500	5.5	>24	0	144	137.9	8.4	+	0	+	+	+
P. R.	Chronic glomerulonephritis	D	1000	6.1	>24	0	120	22.8	91.2	137.8	7.6	8.5	5.60	+	+	+	0	+
P. A.	Nephrosclerosis	D	120	4.0	16	0	100	18.7	109.1	+	+	+	0	0
J. G.*	Disseminated lupus erythematosus	D	inc.	5.5	>24	0	125	24.1	101.0	141.3	+	+	+	0	+
A. C.	Nephrosclerosis	D	inc.	6.3	>24	0	321	8.9	84.6	130.0	5.0	16.8	5.60	+	+	+	0	+
G. B.	Nephrosclerosis	D	1050	6.6	>24	0	133	19.1	77.5	122.3	+	+	+	+	+

The groups in which cardiotoxic effects of potassium were and were not found were comparable except for marked elevations in concentration of serum potassium in the former. inc. = incontinent; + = present; 0 = absent; D = died; R = recovered.

* Autopsy.

† Serum potassium at death was 8.7 mEq./L.

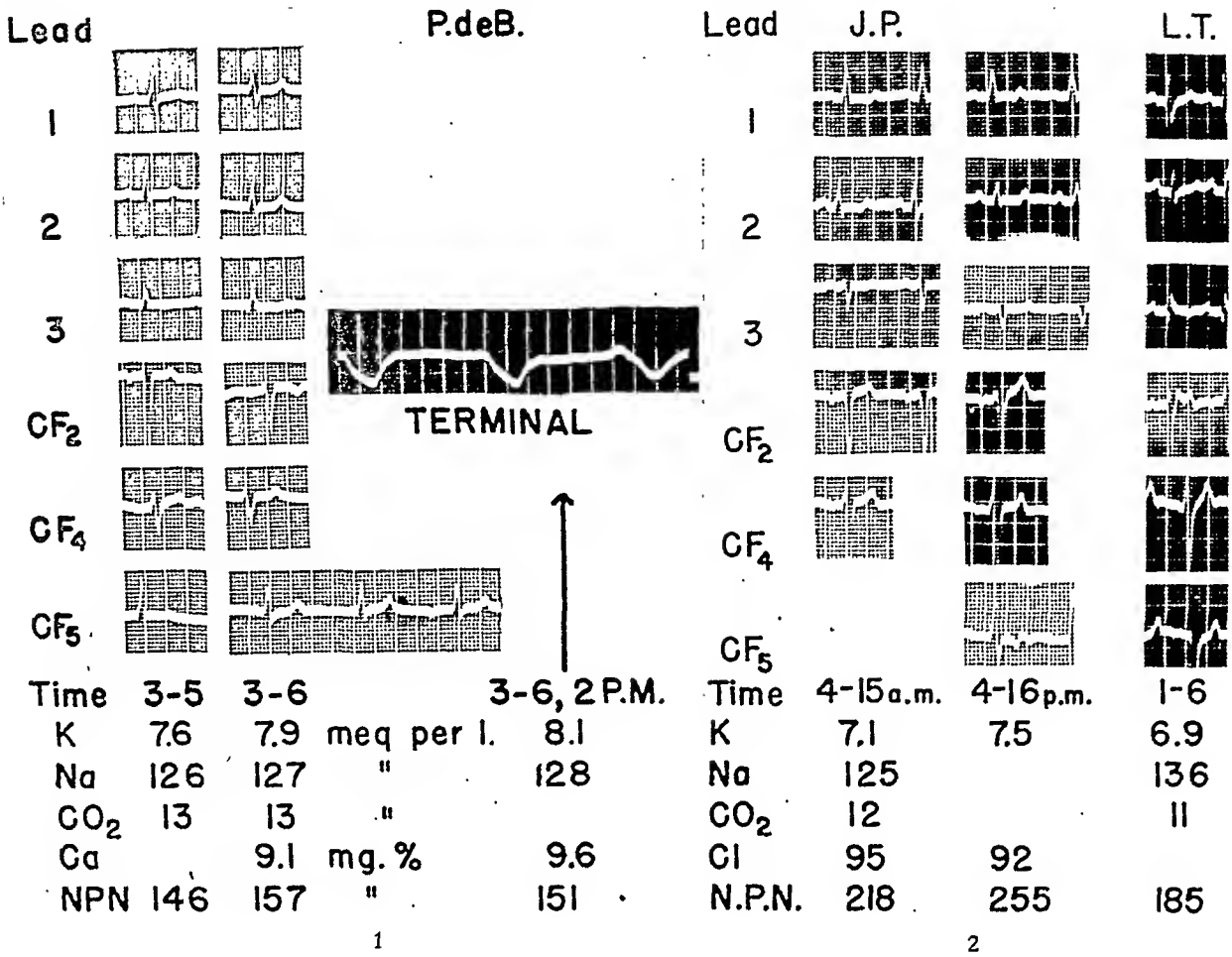


FIG. 1. Potassium effect consisting of absent P waves, increase in duration of QRS and peaked T waves was first evident on the morning of 3-6. At death cardiac arrest preceded respiratory arrest. Three ventricular complexes were registered in lead 1 just prior to death. In this and in subsequent figures the concentrations of serum calcium and of blood non-protein nitrogen are given in mg. per cent. Other concentrations are expressed in mEq./L.

FIG. 2. Possible effect of potassium in J. B. became evident on 4-16, ten hours before death. Increase in P-R interval, slight increase in duration of QRS and peaked T waves occurred. The tracing of L. T. is that taken twelve hours before death; there is no definite evidence of the toxic effect of potassium. The serum potassium at death was 8.7 mEq./L.

Results. The data are presented in Tables 1 and 11 and in Figures 1 to 8.* The entire group of nineteen cases of renal insufficiency was analyzed with respect to features which may produce electrocardiographic abnormalities. (Table 1.) Electrocardiographic disturbances consistent with the effects of a high concentration of serum potassium were observed in four of the nineteen cases. These four differed from the other fifteen apparently only with respect to the presence of marked elevation of serum potassium in the former group.

✓The principal electrocardiographic abnormalities referable to elevation of concentration

* The concentrations of serum calcium and of blood non-protein nitrogen are expressed in milligrams per cent. Other concentrations are expressed in mEq./L.

of potassium were peaked T waves and increase in the duration of the QRS complex. (Figs. 1 to 4.) The peaked T waves were not always abnormally large in amplitude. They were usually upright in the limb leads but occasionally were negative in the CF leads. Depression or occasional elevation of the S-T segment was sometimes noted in patients not receiving digitalis. (Figs. 3 and 4.) Increase in the P-R interval and, in one instance, actual disappearance of the P wave (Fig. 1) occurred as the concentration of serum potassium rose. Changes in the ratio of the deflections of R/S were minimal. These findings were similar to those described previously in cases of potassium intoxication.^{3,9,10,13}

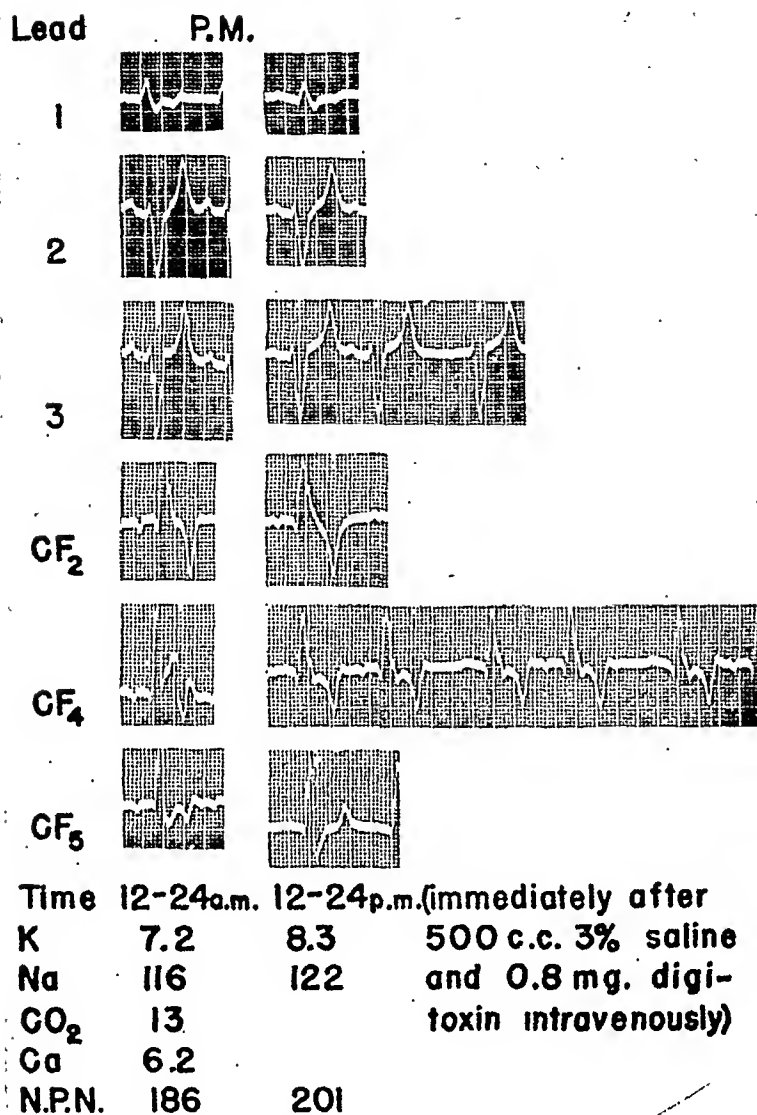


FIG. 3. Striking electrocardiographic evidence of the cardiotoxic effects of potassium; tracings taken eighteen and six hours before death. No digitalis compound had been given prior to 12-24 p.m. The appearance of the electrocardiogram was not improved by administration of saline and 0.8 mg. of digitoxin.

Electrocardiographic findings in relation to concentrations of serum potassium are presented in Table II and are taken from the data of Figures 1 to 4. The electrocardiographic effect of a given elevated concentration of serum potassium was variable. There were advanced electrocardiographic disturbances at a concentration of 7.2 mEq./L. as seen in one case. (Fig. 3.) No effect was apparent at 7.6 mEq./L. in another. (Fig. 1.) The action of potassium was observed at 6.8 mEq./L. in R. S. (Fig. 4) but could not be demonstrated at 6.9 mEq./L. in L. T. (Fig. 2.) The intensity of effect on the electrocardiogram in the group as a whole was

not directly proportional to the concentration of potassium in serum. Increasing electrocardiographic effect in a given patient, however, was associated with increases in concentration of potassium. (Table II, Figs. 1 to 4.)

No toxic action of potassium was found at concentrations of serum potassium below 6.8 mEq./L. Cardiotoxic findings were sometimes present between 6.8 and 7.6 mEq./L. Cardiotoxic action was found regularly at concentrations greater than 7.8 mEq./L.

The electrocardiographic abnormalities referable to potassium were striking, and occurred at lower concentrations of serum potassium in

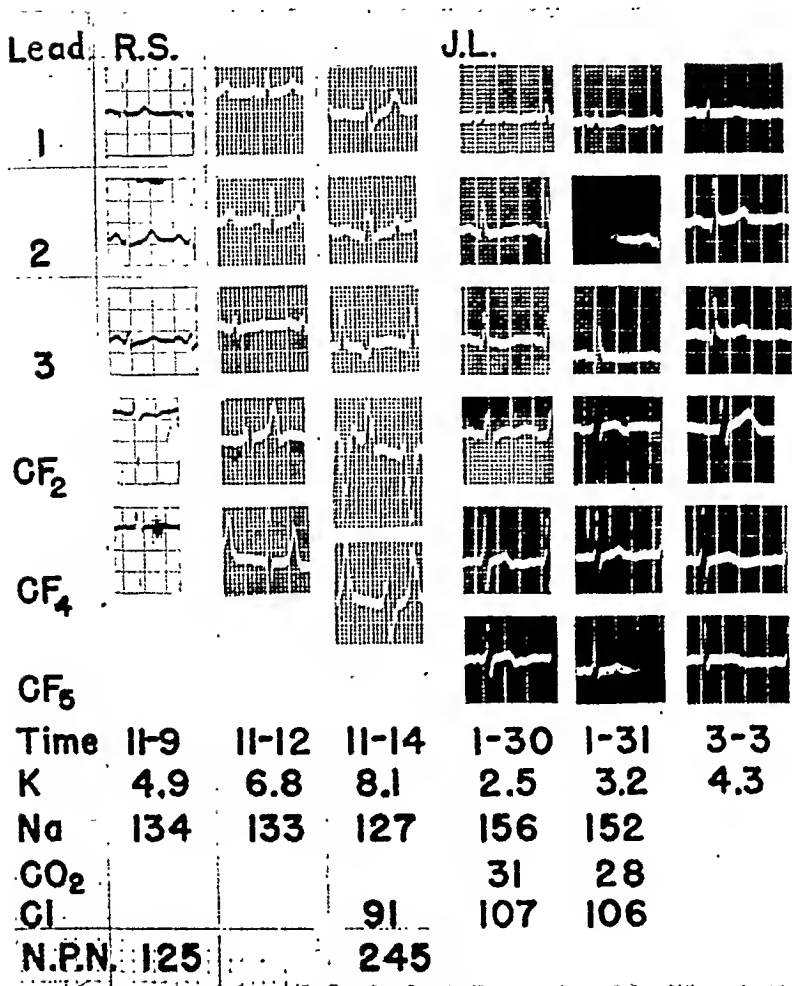


FIG. 4. In R. S. potassium effect was definitely present on 11-12. By 11-14, two hours before death, these effects had become more pronounced; no digitalis compound had been given. J. L. had been operated upon for carcinoma of the colon and had developed deficit of potassium in the post-operative period. On 1-31 despite an increase in concentration of serum potassium there was no appreciable change in the E.C.G. By 3-3, coincident with an increase in serum potassium, T waves in most of the leads had increased in amplitude. No digitalis compound had been given.

the two patients who were not digitalized. (Figs. 3 and 4.) One of the digitalized patients was followed for one week prior to death. (Fig. 1.) The serum potassium rose from 6.4 to 8.1 mEq./L. at death. Potassium effect appeared at 7.9 mEq./L. Three grossly disorganized, extremely prolonged ventricular complexes were recorded just before death. Cardiac arrest preceded respiratory arrest. In this patient slight increases in serum potassium were associated with striking changes in the electrocardiogram.

The data do not permit generalizations with respect to the effects of alterations in pH, serum calcium or sodium on the intensity of the potassium effect. In one instance infusion of hypertonic saline did not ameliorate the elec-

trocardiographic abnormalities. (Fig. 3.) The toxic effect of potassium was found only in oliguric patients but there were some oliguric patients in whom abnormally high concentrations of serum potassium were not observed. (Table I.)

The principal electrocardiographic findings referable to low concentration of serum potassium were low amplitude of the T waves and prolongation of the Q-T interval. (Figs. 4 to 8.) These findings were present in a case of renal insufficiency with abnormal depression of the serum potassium. (Fig. 5.) There was no consistent relationship between changes in serum potassium and changes in the electrocardiogram. Since concentrations of serum calcium

were not determined, no conclusions can be drawn with respect to changes in electrical systole. Digitoxin was given after the tracing of March 21st.

The four patients with low concentrations of serum potassium and normal renal function had

TABLE II

RELATIONSHIP OF ELEVATED CONCENTRATION OF SERUM POTASSIUM TO EFFECT ON THE ELECTROCARDIOGRAM

Serum Potassium mEq./L.	Patient	E.C.G. Evidence of Effect of Potassium		
		None	Moderate	Pro-nounced
6.8	R. S.	..	+	
6.9	L. T.	+		
7.1	J. P.	+		
7.2	P. M.	+
7.5	J. P.	..	+	
7.6	P. DeB.	+		
7.9	P. DeB.	+
8.1	P. DeB.	+
8.1	R. S.	+
8.3	P. M.	+

At concentrations of serum potassium below 7.9 mEq./L. at least, E.C.G. findings cannot be accurately predicted simply from knowledge of these concentrations.

been sustained on parenteral fluids containing no potassium. Deficit of potassium was produced by losses of the ion in the urine and in gastrointestinal fluids. Concentrations of serum potassium were increased by the slow intravenous administration of potassium salts. One of the patients (M. M., Fig. 6) was suspected of having heart disease (coronary arteriosclerosis) and was digitalized. There was no clinical evidence of heart disease in the others.

The T waves were low in all of the patients initially; these waves increased in amplitude as the serum potassium rose in two of the patients. The increase in serum potassium was moderately and markedly correlated, respectively, with increased height of the T wave in J. L. (Fig. 4) and A. M. (Fig. 7.) The T wave changes were not clearly related to increase in concentration of serum potassium in the other two cases. (Figs. 6 and 8.)

Prolongation of the Q-T interval occurred in three of the four patients when the concentration of serum potassium was low. (Figs. 6 to 8.) Disappearance or persistence of this abnormality

was not definitely related to a rise in concentration of serum potassium to within the normal range. Disturbances in the P-R interval and in the height of the S-T segment were not striking features of the electrocardiograms.

COMMENTS

The electrocardiographic findings of potassium intoxication were present only when the concentration of serum potassium was elevated. High concentrations of serum potassium with associated cardiac disturbances reflected in electrocardiographic abnormalities may have been factors contributing to the death of four of nineteen patients with severe renal insufficiency. This incidence is inconsistent with the view that potassium intoxication is an extremely rare event in patients dying of renal insufficiency.¹⁴ It supports the hypothesis, which was based on electrocardiographic evidence alone, that the cardiotoxic action of potassium occurs more frequently than is ordinarily suspected in patients dying of renal insufficiency.¹⁵

There were numerous measurements of concentrations of serum potassium between 6.0 and 7.0 mEq./L. in this study. Since in one patient peaked T waves were noted between 6.5 and 7.0 mEq./L., this range is an approximation of the lowest concentrations at which cardiotoxic results of potassium could be demonstrated. The lowest corresponding concentration of serum potassium found under different circumstances in the dog was 5.0 mEq./L.^{1,2} Peaked T waves were the first sign of elevation of serum potassium both in this study and in the dog.^{1,2} Subsequent disturbances in the QRS interval, P-R interval, S-T segment and P waves were found to occur concurrently in the present study.

Although in a given patient increase in the severity of electrocardiographic disturbance was associated with abnormal elevation in the concentration of serum potassium, the appearance of the electrocardiogram at elevated concentrations of serum potassium differed widely from case

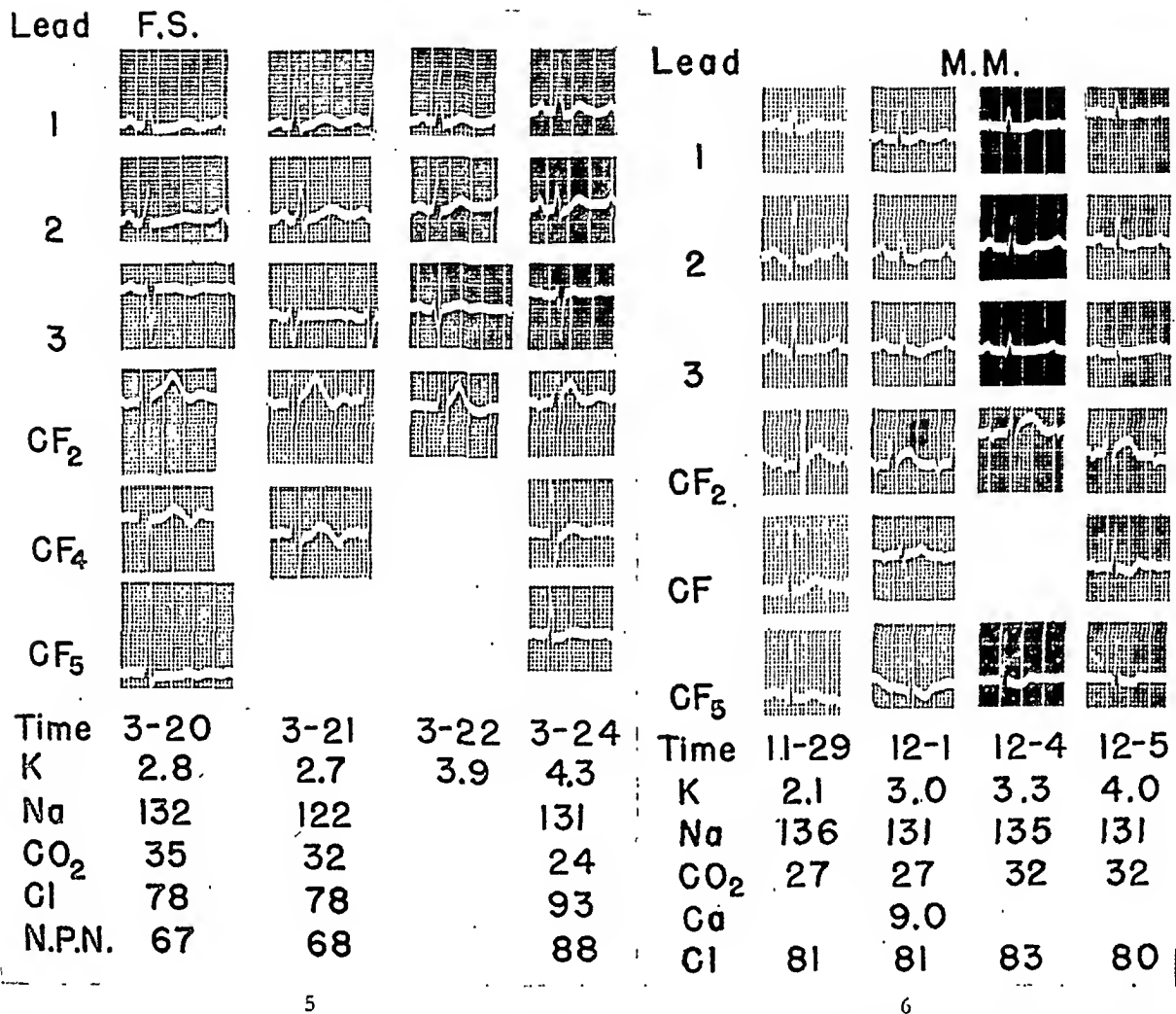


FIG. 5. Case of renal insufficiency with low serum potassium. There is no demonstrable relationship between changes in the concentration of serum potassium and changes in the E.C.G. Digitoxin was given after the tracing of 3-21. FIG. 6. The patient had cirrhosis of the liver. Intake had been low in potassium for several weeks. There is no demonstrable relationship between changes in the concentration of serum potassium and changes in the electrocardiogram; digitoxin had been given.

to case. Comparable differences were disclosed to a certain extent in fundamental studies of the cardiotoxic action of potassium in the dog.^{1,2} Therefore, an evaluation of the relation between hyperkalemia and actual cardiac damage apart from that estimated from the electrocardiogram is appropriate. There may be considerable discrepancy between the degree of cardiac disease as evaluated by clinical and pathologic criteria and the degree of electrocardiographic disturbance.^{4,6} Hoff, Winkler and Smith have shown that during stimulation of the vagus of the dog comparatively slight elevations of the concentration of

serum potassium may result in temporary cardiac arrest without advanced electrocardiographic disturbances consistent with potassium effect.¹⁷ Under certain circumstances the cardiac damage related to elevated extracellular concentration of potassium may exceed the degree of observed electrocardiographic disturbance. This may apply particularly to patients with renal insufficiency since numerous factors may reinforce or mask abnormalities in the electrocardiogram. Conversely, it is possible that the degree of cardiac disturbance related to the effect of potassium may appear spuriously great if judged solely

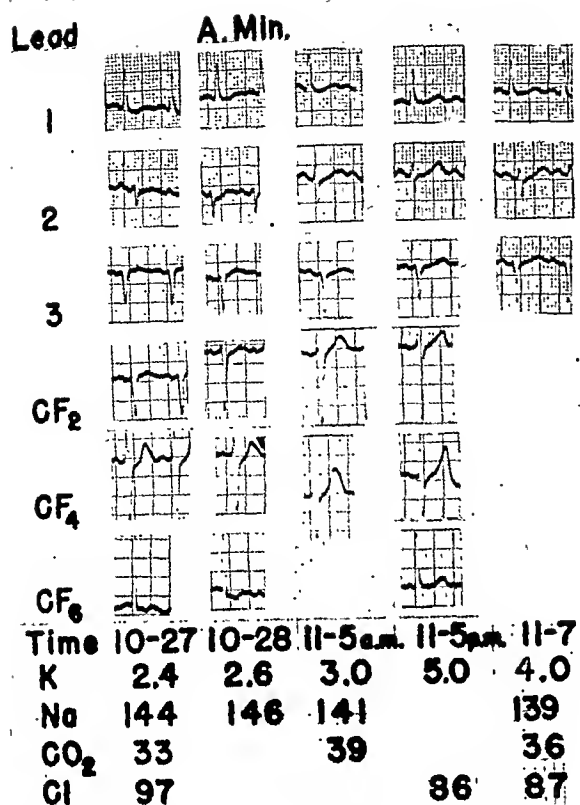


FIG. 7. The patient had been operated on for carcinoma of the common bile duct. There is a direct relation between the height of the T wave and the concentration of serum potassium. Patient had received 6 Gm. of potassium by slow intravenous infusion just prior to the second tracing of 11-5.

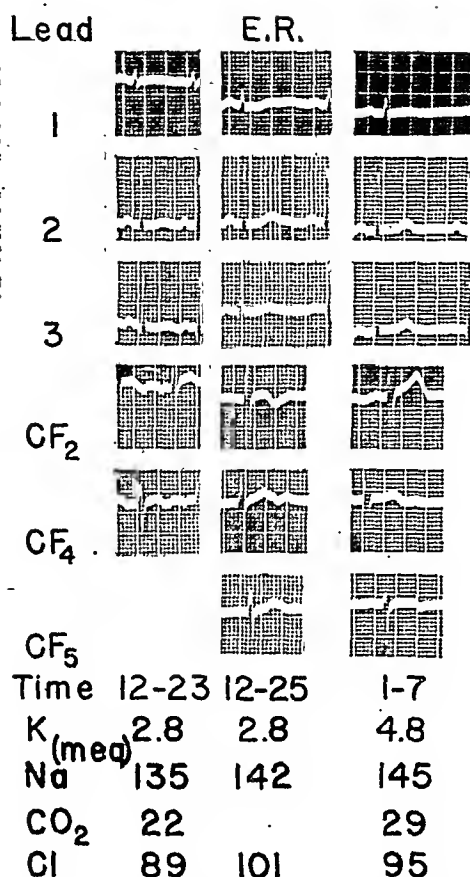


FIG. 8. The patient had intractable vomiting of unknown etiology. There is no definite relation between changes in the concentration of serum potassium and the changes in the electrocardiogram.

by the intensity of the electrocardiographic findings.

The electrocardiographic findings in the present group of cases of low concentration of serum potassium are similar to those described by others.⁴⁻⁸ Changes in these findings were poorly correlated with changes in concentration of serum potassium in three of the five cases. What are possible explanations of this discrepancy? Electrocardiographic disturbances indistinguishable from those of hypokalemia may occur in other states affecting the heart.¹⁶ Digoxin was being given to two of the patients and may have prevented elevation of the T wave when the serum potassium became normal. Aside from other possible sources of damage to the heart it may be that some form of more permanent cardiac damage, which persists after the hypokalemia has been corrected, occurs during deficiency

of potassium. Focal cardiac lesions have been produced in animals by deficits of potassium.¹⁸

The possible value of parenteral therapy with potassium to patients with normal kidneys and cellular deficit of the ion has been emphasized.^{11,15-21} Certain of these patients often in association with dehydration, sodium depletion and peripheral vascular collapse have been found to have elevated concentrations of serum potassium. Based on experiments in dogs,^{1,2} it has been assumed that serious cardiotoxic action of potassium does not occur in man until the concentration of serum potassium reaches 10 to 12 mEq./L.^{19,22} Definite electrocardiographic disturbances related to the effect of extracellular potassium occurred in renal insufficiency in man at serum concentrations of 6.8 to 7.9 mEq./L. in the present study. Neither the present line of

evidence nor that derived from data on the dog can be logically transposed to provide conclusive limits of safety for the administration of potassium to patients without severe renal insufficiency. But the range of dangerous concentrations of serum potassium as defined by the electrocardiographic abnormalities in this group of patients provides an analogy which may be helpful in minimizing the risk of using potassium as a therapeutic agent.

Certain tentative generalizations can be made concerning the place of the electrocardiogram in the control of potassium therapy. When electrocardiographic evidence of the effect of hyperkalemia is present, potassium administration is dangerous. The absence of such evidence at concentrations of serum potassium at which electrocardiographic changes may occur in other patients does not exclude hyperkalemia. The electrocardiogram is not properly a substitute for the measurement of the concentration of serum potassium.

Suddenly appearing flaccid paralyses and other symptoms and signs attributed to both low and high concentrations of serum potassium have been observed in patients not having familial periodic paralysis.^{3,7,8,21,23} These findings were absent in reports of other similar patients and in the present series.^{6,9,10,21,24} Some unknown factors as well as the concentration of serum potassium may play a rôle in the production of the paralysis.

SUMMARY

1. Electrocardiograms and blood samples for simultaneous chemical analyses were taken from nineteen patients with severe renal insufficiency. Similar studies were made in five patients with diminished and, subsequently, normal concentrations of serum potassium.

2. Electrocardiographic findings referable to the toxic effect of potassium were observed in four of the patients with renal insufficiency when the concentration of serum potassium was elevated. These find-

ings were not observed when the concentration of serum potassium was normal.

3. The range of concentration of serum potassium within which associated electrocardiographic disturbances sometimes occurred was 6.8 to 7.6 mEq./L. These disturbances were present consistently at concentrations greater than 7.8 mEq./L. At a given elevated concentration of serum potassium the appearance of the electrocardiogram varied widely.

4. The most characteristic changes associated with hyperkalemia in this series were peaked T waves and increase in the duration of the QRS complex. Low amplitude of the T wave and prolonged electrical systole were the most frequent findings in the group with hypokalemia.

5. In three of the five patients elevation of the concentrations of serum potassium to normal values did not ameliorate the electrocardiographic disturbances which presumably resulted from low concentrations.

6. Implications of the present study for the problem of the use of potassium in treatment have been discussed.

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Influence of the Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis*

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RECENT investigations have related the changes in the electrocardiogram of patients with diabetic acidosis to alterations in certain electrolytes. In early studies Hepburn and Graham,¹ Taterka² and Smith and Hickling³ described certain changes in the electrocardiogram but did not believe they could be attributed to acidosis. In 1934 Klingenberg⁴ studied ten patients with this type of metabolic disturbance and found the electrocardiogram to be normal in only one subject. In 1937 Bellet and Dyer⁵ described changes in the electrocardiogram in patients with diabetic acidosis that were both consistent and reversible. The chief alterations observed by these workers were lengthening in the Q-T interval, depression of the S-T segments and inversion of the T waves. Of particular interest was their observation that these alterations occurred approximately twenty-four hours after insulin therapy had been instituted, at a time when the acidotic state had been relieved by appropriate therapy. Martin and Wertman⁶ found that 43 per cent of their patients with diabetic acidosis who had prolongation of the Q-T intervals showed a low serum potassium or calcium (total or ionized). Their report also emphasized the high degree of correlation between low T waves and low serum potassium levels.

The present report is based on a study of the relationship to and the effect of changes

in the serum potassium and other electrolytes on the electrocardiogram in forty-five patients during and upon emergence from diabetic acidosis.

METHOD AND MATERIALS

The diagnosis of diabetic acidosis was established in each of forty-five patients by the usual clinical criteria; these included a carbon dioxide combining power of less than 14 mEq. and a blood sugar greater than 200 mg. per cent.

Upon admission to the hospital venous blood was taken for determination of the blood sugar,⁷ carbon dioxide combining power,⁸ pH, protein,⁹ chloride,¹⁰ blood urea nitrogen,¹¹ calcium,¹² sodium¹³ and potassium.¹³ Simultaneously an electrocardiogram including leads I, II, III and precordial leads CR₂, CR₃, CR₄ and CR₅ was taken. These studies were repeated at intervals varying from one to twelve hours after the first administration of insulin until the clinical condition, the chemical and the electrocardiographic findings had returned to normal.

These patients all received the same type of therapy, the amount of therapeutic agent being varied according to the severity of the acidosis and the state of cardiovascular embarrassment. All received regular insulin subcutaneously, in divided doses, the total amount varying from 150 to 800 units. All were given at least 2,000 cc. of isotonic sodium chloride by clysis; none received more than 3,000 cc. in the first twelve hours. The total amount of fluid administered during the first twenty-four hours did not exceed 6,000 cc. although most received 3,000 cc. In addition sodium bicarbonate was administered

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to most patients. Two routes were utilized to administer the bicarbonate; most patients received 16 Gm. of the sodium salt in 2 Gm. doses orally every twenty minutes; others received 11.25 Gm. dissolved in 500 cc. of distilled water via the intravenous route. When the blood sugar had decreased to 250 mg. per cent, glucose was administered in 25 Gm. portions via the Levine tube; the total dose depended upon the blood sugar level. Shock was treated by administration of plasma and occasionally whole blood.

Potassium chloride was administered parenterally to twelve patients as an isotonic solution (1.14 per cent) in the period following therapy of the acidosis when the serum potassium was low. This solution was given by the oral route in five additional cases. The effect of the administration of potassium chloride was correlated in these patients with the chemical and electrocardiographic findings.

OBSERVATIONS

Alterations in the Serum Potassium in Patients with Diabetic Acidosis. In 1946 Holler¹⁴ reported the occurrence of a low serum potassium accompanied by clinical manifestations associated with the "syndrome of hypopotassemia"* during the treatment of a patient with diabetic acidosis. Administration of potassium to this patient reversed the respiratory distress, flaccid muscle paralysis and the cardiovascular alterations including the electrocardiographic changes.

* The "syndrome of hypopotassemia" is used to refer to the clinical syndrome which manifests itself in patients with familial periodic paralysis²⁴⁻²⁶ and diabetic acidosis.^{14,17,28} The signs and symptoms which occur when the potassium of the body is depleted are limited to disturbances in the skeletal muscle and cardiovascular system.

During a crisis all of the striated muscle of the body becomes flaccid. Patients show a gasping type of respiration due to paralysis of the diaphragm and intercostal muscles. The respiratory paralysis may result in death of the patient. The cardiovascular manifestations have been best described by Frenkel.²⁸ They include such signs and symptoms as an increase in the pulse pressure, low diastolic blood pressure, collapsing pulse, increase in cardiac dullness, systolic murmur, high venous pressure and profound electrocardiographic alterations. Administration of potassium to these patients by the oral or intravenous route results in the disappearance of all signs and symptoms.

Atchley, Loeb, Richards, Benedict and Driscoll,¹⁶ Butler, Talbot, Burnett, Stansbury and McLachlan¹⁷ have shown that the total body potassium concentration is below normal before therapy is started in patients with diabetic acidosis. These well established facts concerning the level of the total body potassium are in contrast to the findings of the concentration of the *serum* potassium in patients with diabetic acidosis. Martin and Wertman¹⁵ first showed that the serum potassium was often elevated before insulin therapy was instituted in patients with diabetic acidosis.

Figure 1 indicates the findings in the forty-five patients in our series with diabetic acidosis. The serum potassium level is plotted against the hours before and after therapy was instituted. It will be noted that before therapy the serum potassium level varied from a normal concentration of 5 mEq. to a markedly elevated concentration of 9.3 mEq. Thus, in spite of a low total body potassium concentration before therapy in patients with diabetic acidosis, the serum level of this cation is found to be normal or elevated.

On the other hand, as can also be observed from Figure 1, as early as two hours after the first injection of insulin, but more commonly between the third to eighteenth hour, the serum potassium level rapidly drops to a concentration below normal. This observation was constant throughout our study and is of particular importance since it is at this time that the blood sugar level and the carbon dioxide combining power approach normal limits. The clinical condition of the patient at this time was often more critical than before therapy was begun. Also, as will be shown later, the electrocardiogram, which on initial study presented a normal configuration or one usually associated with a high serum potassium, presented the typical findings associated with a low serum potassium. Finally the data of Figure 1 show that the serum potassium levels in these patients remained below normal unless potassium chloride or a diet other than glucose was administered.

Electrocardiographic Findings Associated with High and Low Serum Potassium Levels. The typical electrocardiographic findings usually associated with a high and low serum potassium concentration are shown in Figure 2. The serum calcium (total and

potassium level was elevated to 7.3 mEq. The T wave is seen to be increased in amplitude with a narrow base. The Q-T interval²³ is not prolonged.

The electrocardiographic pattern associated with a low serum potassium was

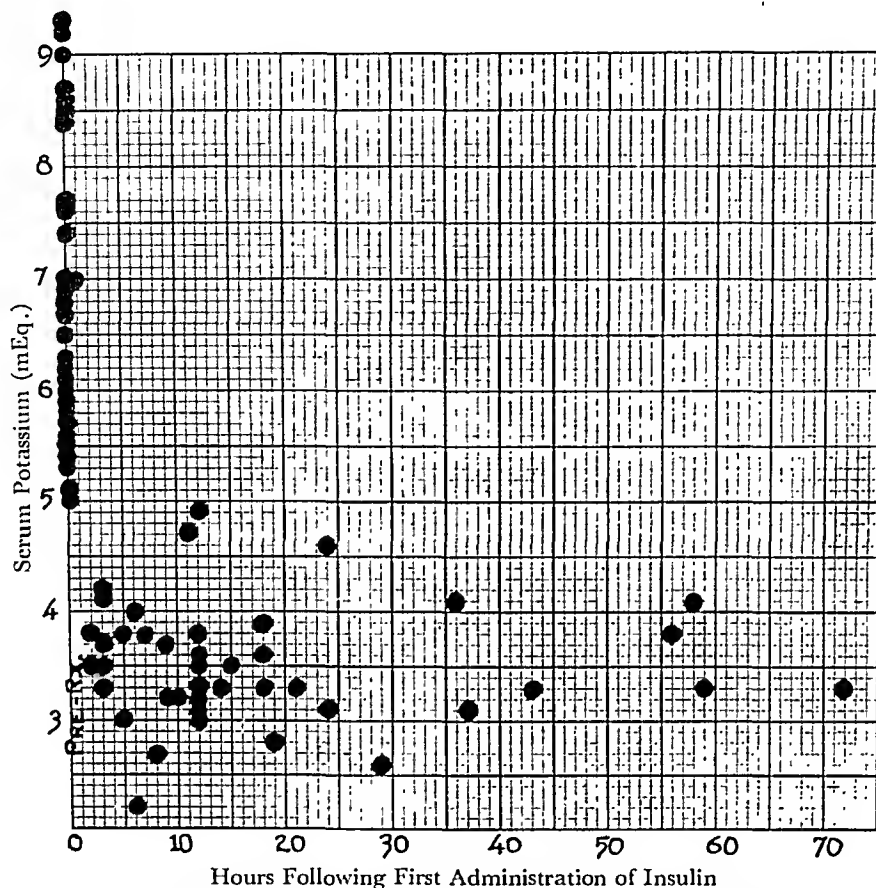


FIG. 1. A composite graph showing the serum potassium concentration of forty-five patients with diabetic acidosis. The serum potassium levels are plotted against the hours following the first administration of insulin. Before therapy the serum level of this cation is normal or elevated. In the period of two to eighteen hours after treatment was instituted, the serum potassium had decreased to levels below normal. The serum potassium did not return to normal until potassium chloride or a diet other than glucose was administered.

ionized) was normal when both tracings were taken. The electrocardiographic changes associated with an elevated serum level of potassium have been described by Winkler, Hoff and Smith¹⁸ in dogs, by Keith, Burchell and Baggenstoss¹⁹ in patients with uremia and by Martin and Wertman⁶ in patients with diabetic acidosis. The upper tracing in Figure 2 shows the findings characteristically present in a patient with diabetic acidosis before therapy. The serum

described initially by Stewart, Smith and Milhorat²⁰ in patients with familial periodic paralysis. The electrocardiographic findings in patients with diabetic acidosis were described in 1937 by Bellet and Dyer;⁵ recently these changes have been attributed to a low concentration of potassium by Holler¹⁴ and Martin and Wertman.⁶ Similar changes have recently been observed by us in patients with intestinal obstruction.²¹ The lower tracing in Figure 2 is illustrative

of the typical configuration found when the serum level was decreased to 3 mEq. at the time the tracing was obtained. The Q-T interval²³ is now prolonged and the T wave is inverted. These findings, with minor modifications, were constantly present throughout our study of patients with diabetic acidosis.

Effect of the Serum Potassium on the Q-T Interval. Correlation studies: Since the Q-T interval was found to be constantly prolonged after treatment had been instituted in those with diabetic acidosis and since this change appeared to be reversible, the etiology of this finding was investigated. Correlation studies were made of the percentage of increase above normal in the duration of the Q-T interval and the serum levels of certain of the electrolytes. The best relationship is found to exist between the percentage above normal in the duration of the Q-T interval and the serum potassium concentration. Figure 3 shows that a high coefficient of correlation,^{29,30} namely, minus 0.73 is found between the percentage of increase in the Q-T interval above normal and the serum level of this cation. When a partial coefficient of correlation^{29,30} was determined, keeping the serum calcium normal, the coefficient value was minus 0.92 which is highly significant.

Since the Q-T interval is known to be influenced to a large degree by the heart rate, the serum potassium level was compared with the Q-T interval at a time when the cycle length was constant. It will be noted (Fig. 4) that a high degree of correlation was found. These studies suggest that a definite relation exists between the serum potassium and prolongation of the Q-T interval. Further studies are needed to elucidate the cause of this relationship.

In the patients studied the coefficient of correlation^{29,30} was determined also between the percentage of increase in the duration of the Q-T interval above normal and the serum calcium level and between the former and the carbon dioxide tension. In neither case was the relationship significant.

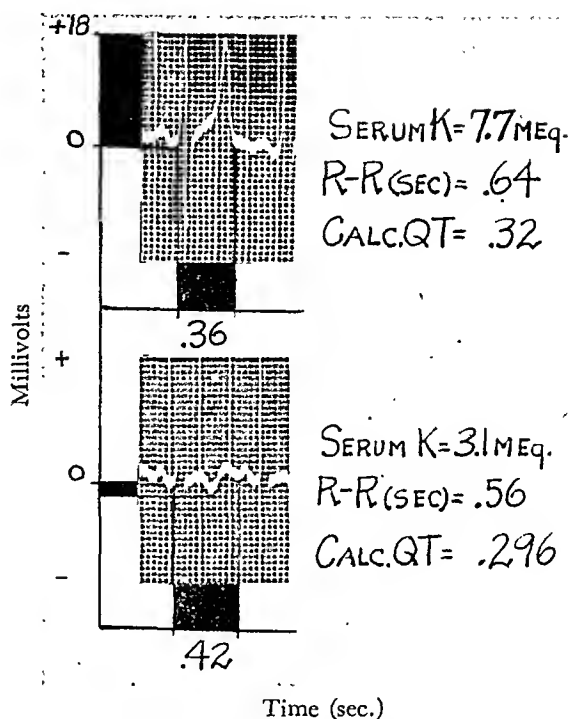


FIG. 2. Electrocardiographic records taken on patient with diabetic acidosis in the precordial lead CR₃. The upper tracing was obtained before therapy was instituted at which time the serum potassium level was elevated. The lower tracing was taken a short time after treatment was begun when the serum potassium had decreased to a level below normal. The serum calcium (total and ionized) was normal when both electrocardiograms were obtained.

Effect of Intravenous Potassium on the Q-T Interval. In an effort to study the effect of the serum potassium concentration on the Q-T interval, potassium chloride was administered to patients with diabetic acidosis at a time when the electrocardiogram showed changes suggestive of a low serum potassium. Figure 5 is illustrative of a typical instance. It will be noted that when the serum level of this cation has decreased to 4.4 mEq., the Q-T interval was prolonged by 23 per cent above the calculated normal value. After administration of 450 cc. of potassium chloride (isotonic solution), the Q-T interval became normal in duration. More important was the observation that when 50 cc. of potassium chloride were administered quickly, namely, in seven minutes the Q-T interval rapidly became shorter in duration. This figure also shows that shortly after the potassium chloride was discontinued the

Q-T interval, which had been normal, rapidly became prolonged. This finding was constant in the twelve patients studied in this manner. Since these observations indicate that the Q-T interval underwent alteration at a time when the potassium

caused these alterations in the Q-T interval since this cation would be increasing inside the cell both during the administration of potassium chloride and after it had been discontinued.

The Q-T interval may also be prolonged

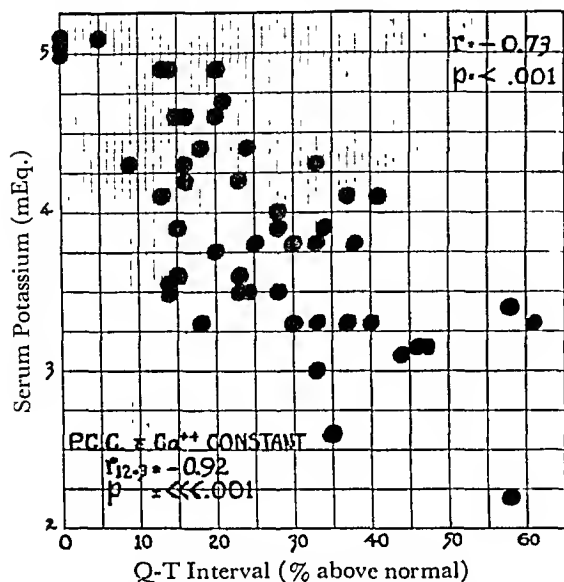


FIG. 3. Composite graph of results taken from forty-five patients with diabetic acidosis. The serum potassium level is compared to the percentage above normal in the duration of the Q-T interval. The coefficient of correlation (r) was minus 0.73; this value indicates that a significant relation exists between these two factors. In the lower left hand corner of this figure the partial coefficient of correlation obtained when the serum calcium was kept constant is represented. The value of minus 0.92 indicates that a highly significant relationship exists between the serum potassium concentration and the percentage above normal in the duration of the Q-T interval when the serum calcium is kept constant.

level in the serum changed, they suggest that the duration of electrical systole (Q-T interval) is influenced to a great extent by the serum potassium level in patients with diabetic acidosis.

The possible relation of changes in intracellular potassium to alterations in the Q-T interval must be considered at this point. Since it has been found that the potassium which disappears from the serum cannot be accounted for in the urine or feces, it is logical to assume that it enters the intracellular compartment. Changes in intracellular potassium could not have

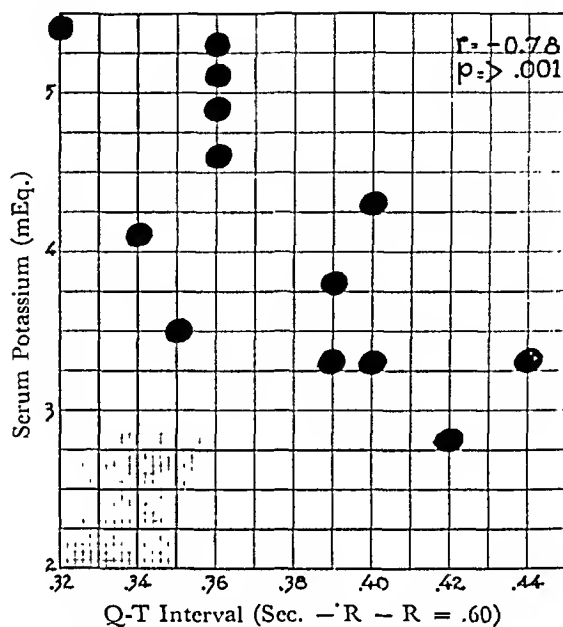


FIG. 4. Composite graph showing relation of serum potassium and Q-T interval in patients receiving active therapy for diabetic acidosis when the heart rate or cycle length (R-R) is kept constant. When the coefficient of correlation (r) was determined, a value of minus 0.78 was found indicating a highly significant relationship exists between these two factors.

by a low serum calcium.²² In hypocalcemia the T wave itself is not involved in the prolongation of the Q-T segment; this is due entirely to lengthening of the isoelectric period between the end of the QRS and the beginning of the T wave. In hypopotassemia, however, prolongation of the Q-T interval involves the T wave proper which is widened. (Fig. 5.)

These results differ from those reported by Martin and Wertman⁶ who found that in only 43 per cent of their patients with prolonged Q-T interval could the prolongation be explained by a concomitant low serum concentration of potassium or calcium. We found in our group of patients that the serum calcium (both total and ionized) was decreased only in the few in-

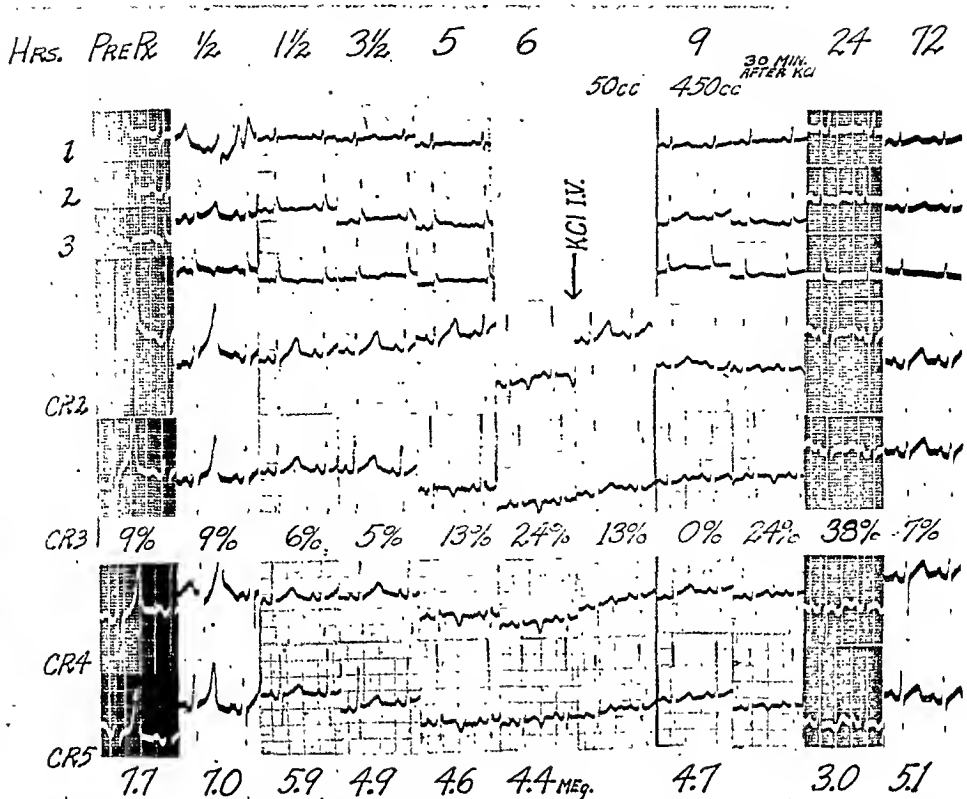


FIG. 5. Electrocardiographic records of leads 1, 2, 3 and precordial leads CR₂, CR₃, CR₄ and CR₅ taken in a patient before and after institution of routine therapy for diabetic acidosis and before and during administration of isotonic potassium chloride. Numbers in the upper part of the figure record the hours after routine therapy was begun. The arrow indicates the time when isotonic potassium chloride was started. The percentage values in the center of the figure represent the calculated percentage of increase above normal of the Q-T interval in the CR₃ position. Numerals under each tracing in the lower part of the figure record the serum potassium level in millequivalents at the time the tracing was taken.

stances when the patients had been in alkalosis for a period of forty-eight hours or longer; when alkalosis existed, the serum potassium level, in addition to the serum calcium concentration, was below normal. Electrocardiograms taken at this time showed a more marked prolongation of the Q-T interval than was found when the potassium concentrations alone were decreased. Additional proof that the level of serum calcium (total or ionized) does not influence the prolongation of the Q-T interval to a great extent in the patients who form the basis for this report is our observation that in five cases intravenous administration of calcium gluconate did not shorten the Q-T interval at a time when it was prolonged.

One other point is deserving of emphasis: the changes in the Q-T interval are most characteristic in the precordial leads in

contrast to the limb leads. The T waves are often isoelectric in the limb leads when the Q-T interval is prolonged, making it difficult to measure the length of electrical systole. Of the precordial leads CR₃ has proved to be the most informative. ✓

Factors Related to the Height of the T Wave.
Correlation studies: The relationship between the height of the T wave and certain constituents of the blood was investigated. Figure 6 shows that a highly significant correlation existed between the height of the T wave and the blood pH. Correlation of the serum potassium concentration and the height of the T wave was significant only when the plasma concentrations of this cation were elevated. Figure 7 shows, however, that a significant correlation was found when the height of the T wave and the carbon dioxide tension was analyzed in these patients. Since changes which affect

the carbon dioxide tension and the blood pH are determined by alterations which occur both intra- and extracellularly, these findings suggest that the height of the T wave is probably controlled by changes which take place both inside and outside

tude or inverted. This is in agreement with Martin and Wertman⁶ who found that some correlation existed between decreased amplitude of the T wave and low serum potassium levels.

A typical example of the behavior of the

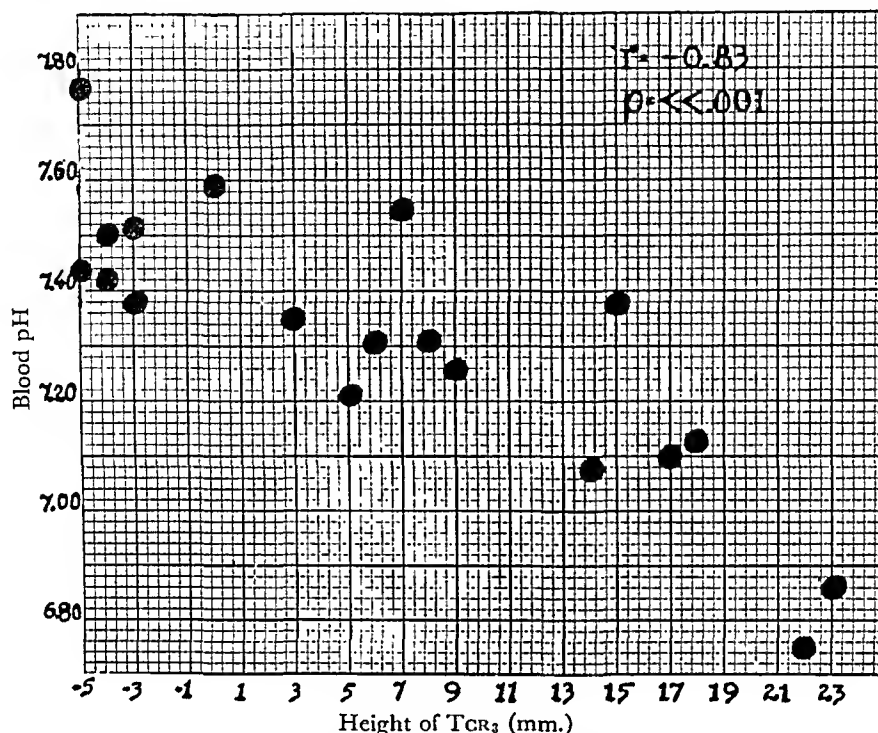


FIG. 6. Composite graph determined in patients before and during therapy for diabetic acidosis. The blood pH is compared to the height of the T wave in millimeters as found in precordial lead CR₃. The coefficient of correlation value (r) was minus 0.83, indicating that a highly significant relationship exists between these two factors.

of the myocardial cell at any given time. This is a very complicated mechanism and a more detailed explanation must await further study.✓

Effect of Intravenous Administration of Potassium Chloride on the Height of the T Wave. In spite of the poor quantitative relation between the serum potassium and the height of the T wave, observations on the effect of intravenous potassium chloride indicate that a definite qualitative relationship exists. When the serum potassium was found to be elevated, the T wave was tall with a narrow base. In contrast, when the serum potassium level was below normal the height of the T wave in patients with diabetic acidosis was diminished in ampli-

T wave during administration of potassium chloride is shown in Figure 8. When the T wave was inverted or of diminished amplitude, administration of isotonic potassium chloride increased the height of the T wave. When the serum potassium level became normal, the height of the T wave assumed a normal amplitude.✓ Since this finding was so constant throughout our study, we believe that for practical purposes it can be said that during treatment of patients with diabetic acidosis if the Q-T interval is found to be prolonged, the level of the serum potassium can be crudely estimated from the height of the T wave.✓

✓*Relationship of the U Wave to Serum Potassium.* In a small group of patients with

diabetic acidosis a U wave was found in the electrocardiogram when the serum potassium level was below normal. To our knowledge the U wave has not been previously emphasized as being related to changes in the electrolytes. This relation

with diabetic acidosis was first described by Bellet and Dyer.⁵ They observed that this occurred after therapy had been instituted, at which time the Q-T interval was prolonged and the T wave inverted. This would indicate that the S-T segment

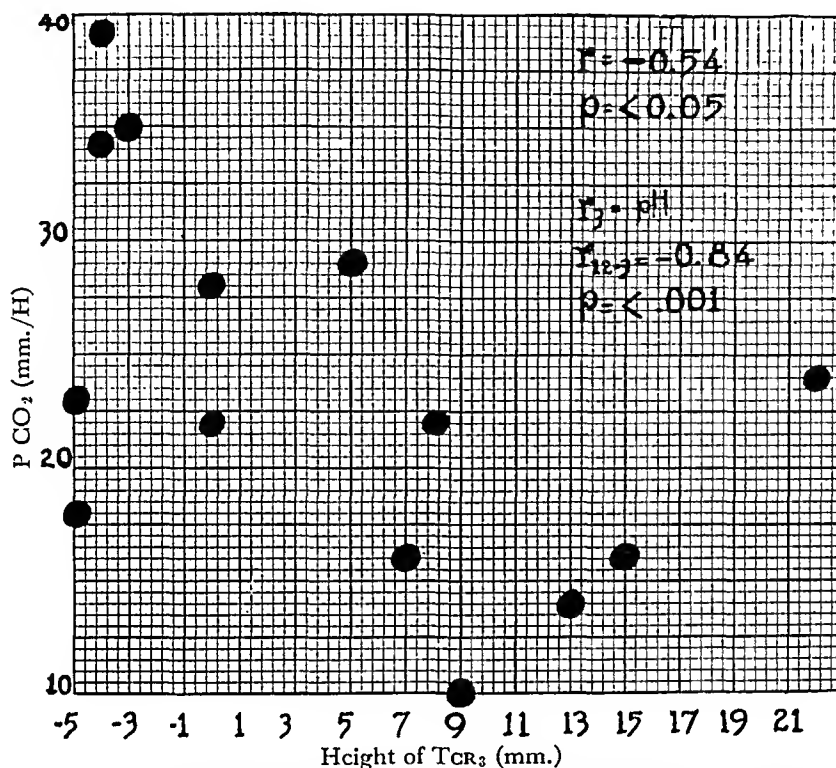


FIG. 7. Composite graph representing the relationship of the carbon dioxide tension and the height of the T wave in the precordial lead CR₃ in patients with diabetic acidosis. The coefficient of correlation value of minus 0.54 indicates that a significant relationship exists between these two factors. There is admittedly a large source of error in these carbon dioxide tension figures since the carbon dioxide combining power was used in lieu of the total carbon dioxide valences in determining the carbon dioxide tensions. The nomogram of Van Slyke and Sendroy³¹ was used to determine the carbon dioxide tensions on these patients.

may be relevant in two ways. (Fig. 8.) First, a U wave when present often made it difficult to measure the Q-T interval since it masked the end of the T wave. Second, a U wave which was present when the serum potassium concentration was below normal completely disappeared during intravenous administration of potassium chloride. This finding was constant throughout our study and suggests that the U wave in these patients was related in some way to a disturbance in the electrolytic balance. ✓

Factors Related to the S-T Segment Depression. Depression of the S-T segment in patients

depression is related in some way to the serum potassium level. Undoubtedly, some relationship may exist; however, about 50 per cent of the patients in our series showed no S-T segment depression when the serum potassium was below normal. Further investigation indicated that the S-T segment depression was related to the degree of cardiovascular shock present in a large group of these patients. Figure 9 is a typical instance. It will be noted that the S-T segment was isoelectric when the serum potassium level was normal and elevated. Six hours after therapy the blood pressure

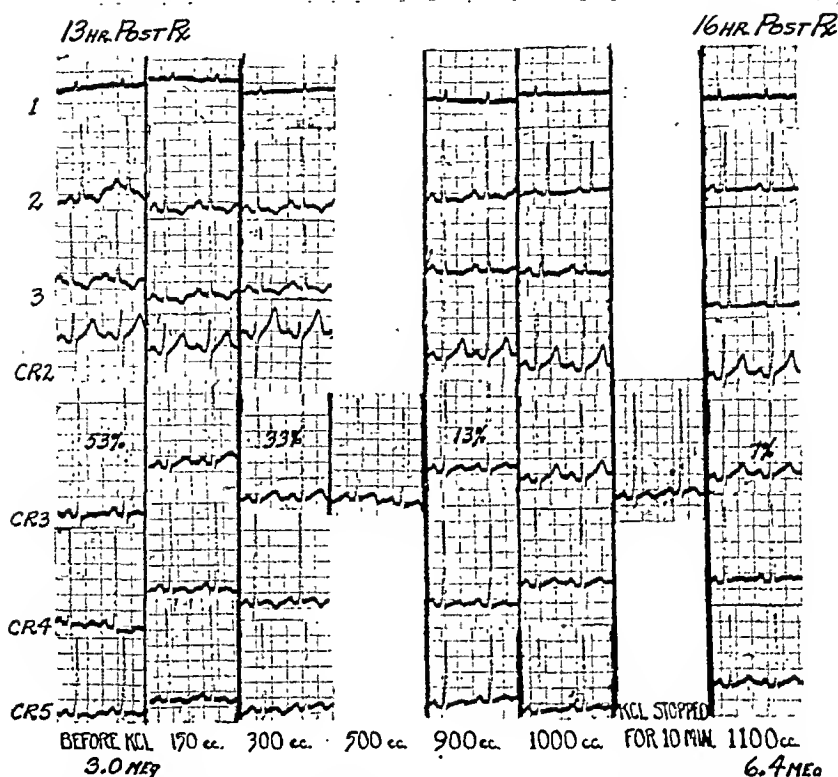


FIG. 8. Electrocardiographic tracings taken before and during the administration of 1,100 cc. of isotonic potassium chloride to a patient being treated for diabetic acidosis. The first tracing was taken thirteen hours after the initial routine therapy for acidosis had been instituted. The serum potassium level was decreased to 3.0 mEq. A tracing was taken after 150 cc., 300 cc., 500 cc., 900 cc., 1,000 cc. and 1,100 cc. of potassium had been administered. The figure shows that the T waves which were inverted in precordial leads CR₂, CR₃ and CR₄ became normal in amplitude after a liter of potassium chloride had been administered and the serum potassium level had risen to the top normal value of 6.4 mEq. Also to be observed is the U wave present in precordial lead CR₄ when the serum potassium level was below normal which disappeared during the administration of potassium chloride. The percentage numbers in the center of the figure represent the percentage above normal in the duration of the Q-T interval at the time the tracing was taken.

decreased to 90/70 and the S-T segment became depressed. Five hours later the blood pressure was 90/38 and the S-T segments were further depressed. The serum potassium level was 4.1 mEq. at this time. During the administration of potassium chloride it will be noted that the blood pressure returned to normal and the S-T segment became isoelectric. ✓

SUMMARY

1. In a study of forty-five patients with diabetic acidosis the serum potassium level was found to be normal or elevated before therapy and fell to concentrations below normal soon after treatment was instituted.

2. Studies are presented which suggest

that the duration of the Q-T interval is influenced for the most part by the level of serum potassium in these patients.

✓3. There was a significant correlation between the height of the T wave and the blood pH and carbon dioxide tension.

4. The height of the T wave is undoubtedly influenced by the serum potassium level. The relationship is only qualitative and in no sense quantitative. Studies are presented which suggest that only in the presence of prolongation of the Q-T interval, when the S-T segments remain normal in duration, can the height of the T wave be used as a crude means of estimating the serum potassium level in patients who are actively treated for diabetic acidosis. ✓

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Sponge Biopsy in Cancer Diagnosis*

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THE histologic diagnosis of cancer is based on surgical biopsy involving surgical removal of a block of tissue from the suspected organ. Efforts toward a cytologic diagnosis of cancer have received considerable stimulus from the extensive and valuable studies of Papanicolau and Traut¹ who demonstrated the usefulness of the cytologic examination of vaginal secretions for the presence of tumor cells in the diagnosis of uterine and especially of cervical cancer.

Certain shortcomings have become apparent in the vaginal smear technic for cancer diagnosis. First, certain tumors, such as adenoma malignum, exfoliate few if any cells into the vaginal secretions. Second, when very few cells are present, a prolonged search of the smear, up to two hours, may be necessary before they are found. Third, the tumor cells form a very small proportion of the total number of cells in the smear, the latter arising from the varied epithelial and glandular surfaces of the female reproductive tract. Fourth, the cells of the vaginal smear have all been exfoliated at an uncertain time prior to the collection of the specimen and have undergone various necrobiotic and autolytic changes leading to many atypical shapes and forms which may be confused with tumor cells or render distinction possible only after considerable special training and experience on the part of the examiner. Fifth, the Papanicolau technic calls for use of an additional series of fixatives and stains beyond those customarily used in routine pathology laboratories.

DESCRIPTION OF THE SPONGE BIOPSY METHOD

The present method represents a simplified technic for obtaining living cells and

clumps of cells in a form suitable for paraffin embedding directly from the tissue suspected. It consists essentially of rubbing a small piece of sponge over the suspected tissue. Fluid and cells exuding from the tissue will be absorbed by the sponge which is then dropped into a small bottle of 10 per cent formalin or other fixative as preferred. The sponge and its absorbed contents are then treated as one would treat a block of tissue for embedding, cutting and staining (hematoxylin and eosin) prior to microscopic examination. A sponge of protein composition such as gelatin is particularly suitable for this purpose because it does not dissolve in the various solvents used in tissue preparation, it has good absorptive powers and is easily cut with the tissue microtome. In our experiments we have used Gelfoam No. 12.* A flat square of sponge 2.0 by 2.0 by 0.5 cm. is clamped along one margin by a surgical sponge forceps. After insertion of a vaginal speculum and visualization of the cervix the sponge is rubbed firmly over the mucosal surface and muco-epithelial junction of the external os to insure liberation and absorption of sufficient material for examination. Each of the two flat surfaces of the sponge is thus rubbed over the tissue so that after fixation and paraffin embedding either surface of the block may be used in sectioning.

It may be seen that the method described attempts to overcome the shortcomings of the vaginal smear technic. The present procedure does not await exfoliation of cells. The latter individually or in clumps are rubbed off and absorbed from the tumor itself. Second, the number of tumor cells

* Manufactured by The Upjohn Company.

* From The Department of Pathology, New York Polyclinic Medical School and Hospital, New York, N. Y.

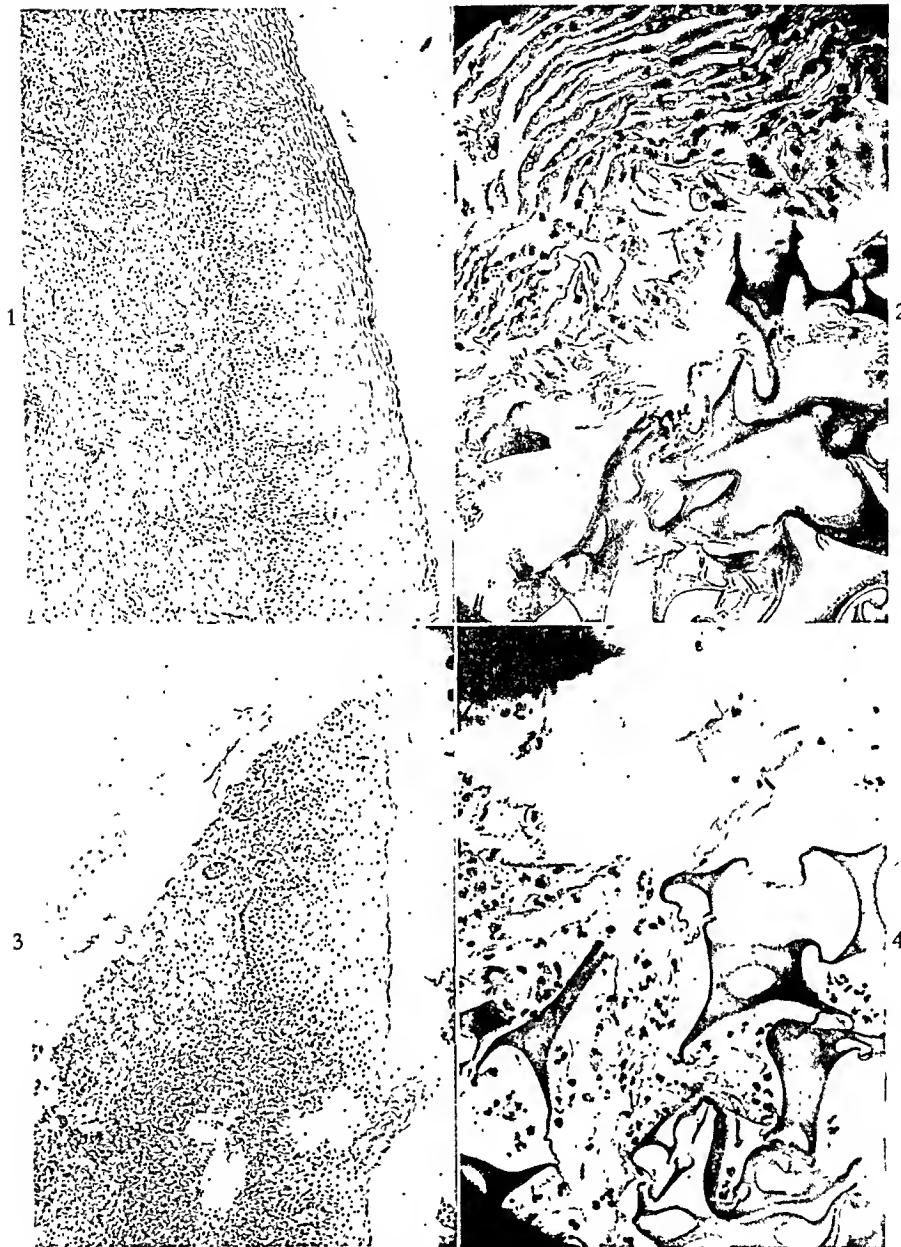


FIG. 1. Surgical biopsy of normal cervix uteri showing surface of stratified epithelium with underlying vascularized fibromuscular tissue. $\times 100$.

FIG. 2. Sponge biopsy of normal cervix (same as Figure 1). The thick, dark strands below represent the gelatin structure of the sponge. Adherent above and in the interstices of the sponge are masses of stratified squamous cells, mostly of the superficial type. $\times 440$.

FIG. 3. Surgical biopsy from cervix showing many inflammatory cells in both superficial and deep zone. $\times 100$.

FIG. 4. Sponge biopsy of inflamed cervix (same case as Figure 3). A few epithelial cells, mucus, and many leukocytes, mononuclear and polymorphonuclear cells are seen. $\times 440$.



FIG. 5. Surgical biopsy from a case of carcinoma of the cervix. The wide zone to the right represents the cancerous tissue. The narrow zone to the left is the fibromuscular tissue of the cervix. Note the large, irregular, darkly-staining tumor cells. $\times 440$.

FIG. 6. Sponge biopsy from same case as Figure 5. In the center of the field is a clump of four tumor cells. Below and to the left are two more tumor cells. Also present are numerous epithelial cells and leukocytes. Note the large size of the tumor cells as well as their nuclei in comparison with the leukocytes. $\times 440$.

FIG. 7. Sponge biopsy from same case as Figure 5. To the right of center is a group of five tumor cells. Epithelial cells, leukocytes and outlines of erythrocytes are also present. $\times 440$.

FIG. 8. Sponge biopsy from same case as Figure 5. A small tissue fragment adherent to the sponge is shown. Below and to the left are inflammatory and necrotic areas. In the center and to the right is a mass of viable tumor tissue. Note the bizarre shapes and large size of many nuclei. Just to the left of center is a nucleus in mitotic division. $\times 440$.

collected is greatly increased and permits of ready detection. Third, practically all cells included are obtained from the tissue under examination. There is practically no admixture of extraneous cells. Fourth, the cells are living cells which are immediately fixed, avoiding disintegrative changes. Fifth, the method employs routine fixatives and stains.

RESULTS

We have examined eighty-eight slides from sponges rubbed over tumorous and non-tumorous tissues. In general the tumor cells when present are so numerous and so readily recognized as to permit prompt diagnosis. The cells are well preserved and well fixed. They show the characteristic changes, large size of cells and nuclei, marked variations as to shape and size, hyperchromatism, anaplasia, atypism and occasional mitoses. Even in the absence of tumor cells the sponge biopsy will give useful information regarding the physiologic or pathologic condition of the surface examined.

The figures represent a series of photomicrographs comparing the findings in sponge biopsy with those of surgical biopsy. (Figs. 1 to 8.) In the normal cervix the sponge merely takes up clumped and individual stratified squamous cells from the mucosal surface. In the inflamed cervix the sponge takes up a considerable amount of mucus with enmeshed mononuclear and polymorphonuclear leukocytes. Epithelial cells, mostly of the superficial type with an admixture of a few cells from the intermediate and deeper epithelial layers, are also found.

In the cancerous cervix the sponge takes up tumor cells individually or in clumps and occasionally small fragments of tumor tissue. The cells are large, irregular, with large, darkly-staining nuclei, sometimes multiple and occasionally in mitosis. Seen in groups or singly, as illustrated, they are readily recognized. Since these tumors are usually ulcerated and infected, one finds leukocytes, polymorphonuclear and mono-

nuclear in type, mucus and erythrocytes. Squamous cells are also present.

COMMENT

The simplicity of the method in respect to gathering, handling and examination of material is such as to encourage further trial. The procedure is adapted to the microscopic examination of the cellular composition of mucous membranes, ulcerative membranes, neoplastic membranes, etc. It is especially useful in the diagnosis of carcinoma of the cervix and may prove applicable in the study of other mucous membranes, e.g., the mouth and pharynx, esophagus, bronchi, rectum, etc.

SUMMARY

A method of sponge biopsy in cancer diagnosis is presented. It consists essentially of absorbing fluid cells and particles of tissue expressed from the surface of a mucous membrane or ulcerating lesion in a suitable sponge. Sponge and contents are treated as a tissue block for fixing, embedding, cutting and staining prior to microscopic examination. The results of sponge biopsy compared to surgical biopsy are illustrated. The method appears to be applicable in the diagnosis of carcinoma of the cervix and may prove applicable in the study of lesions of other mucous membranes that may be reached with a sponge.

ADDENDUM

Subsequent to the completion of this report, the author has successfully applied the method of sponge biopsy in cases of adenocarcinoma of the rectum and sigmoid colon, carcinoma of the corpus uteri, bronchogenic carcinoma of the lung, epidermoid carcinoma of the skin, etc. These lesions were reached by the sponge as required through the proctoscope and sigmoidoscope, vaginal speculum and bronchoscope. Details of procedure and microscopic findings will be published at a later date.

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Use of Intermittent Positive Pressure Breathing Combined with Nebulization in Pulmonary Disease*

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BARACH and his associates¹⁻³ and others⁴ have demonstrated the usefulness of aerosols in the treatment of pulmonary disease. The methods of administration that have been used depend largely on the inspiratory effort of the patient to carry the aerosol into the lungs. However, in some patients adequate dissemination of aerosol may be prevented by physical limitations of breathing, such as obstruction, emphysema, fibrosis and impaired movement of the diaphragm. In the present study an automatic intermittent positive pressure breathing respirator has been combined with a nebulizer for administration of vasodilator agents, penicillin and other substances suitable for nebulization. Since intermittent positive pressure breathing increases both the minute volume of ventilation and the respiratory excursions, it seemed likely that the vapor from a nebulizer employed with this type of breathing apparatus would be more uniformly distributed through the lung air spaces than by methods dependent on the inspiratory effort of the patient alone. Better dissemination of the aerosol would be expected, particularly in individuals with poor diaphragmatic excursions and shallow breathing. If accumulated secretions block the bronchi and bronchioles, intermittent positive pressure breathing may loosen the plugs and promote drainage.

Intermittent positive pressure breathing (IPPB) as produced by automatic respirators consists of active inflation of the lungs under positive pressure (above atmospheric) during inspiration and of passive deflation during expiration, primarily produced by the elasticity of the lungs and chest wall. The peak mask pressure varies with the line pressure which is adjustable from 0 to 30 cm. of water. When the peak mask pressure is reached, cycling of the respirator interrupts the applied positive pressure and opens the expiratory pathway to atmospheric pressure. The IPPB used in this study produces a small decrease in cardiac output,⁵⁻⁷ but this reduction is less than that which normally occurs in man when changing from the supine to the standing position. Changes in blood pressure in the systemic arteries, right ventricle and pulmonary artery are of small magnitude, there usually being a slight elevation of the mean pressure in each. Hyperventilation may occur with IPPB, but lowering of the arterial $p\text{CO}_2$ can be controlled.⁸ Tetany or its prodromal signs have not been observed during IPPB.^{5,7,8} In patients with physiologic hypoventilation a lowering of the arterial $p\text{CO}_2$ with IPPB indicates an increase in the volume of effective alveolar air.

A pneumatic balance type respirator,⁵ which can be seen in the accompanying

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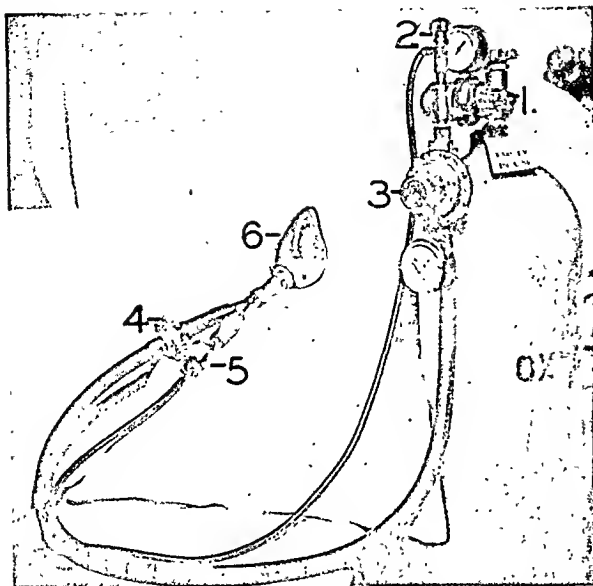


FIG. 1. Complete IPPB apparatus with nebulizer connected. (1) Pressure reduction valve on a high pressure oxygen cylinder; (2) needle valve for supplying pressure to the nebulizer; (3) line pressure valve with an adjustable range from 0 to 30 cm. water; (4) pneumatic balance type respirator; (5) special nebulizer used with the IPPB apparatus; (6) oxygen mask.

illustration, was used to provide IBBP* in the present study. This device is a simple differential pressure valve which changes continuous positive pressure (adjustable from 0 to 30 cm. of water by the regulator on the oxygen cylinder) into an intermittent positive pressure, thus functioning as a respirator capable of producing effective artificial respiration in the apneic subject (6 to 10 liters per minute).⁵ In this study the line pressure of the IPPB apparatus was set at 20 cm. of water. This respirator follows the slightest breathing effort of the conscious subject and unlike most automatic respirators the cycling pattern is not fixed. These features permit easy, comfortable and almost effortless breathing in the conscious patient if a suitable type face mask be used.

A nebulizer (seen in the illustration) was constructed of heavy clear plastic with a stainless steel nebulization mechanism which could be removed for cleaning and adjustment. Other nebulizers commercially avail-

able, although more fragile and difficult to clean, can be used with this arrangement. The gas pressure for operating the nebulizer was obtained by connecting a needle valve, between the first and second stage reduction valves on the oxygen regulator of the IPPB apparatus, with a piece of small-bore rubber tubing to the nebulizer. (Note photograph.) This arrangement provided a controllable pressure greater than the line pressure used for the IPPB and thus prevented backflow in the nebulizer during inspiration. The nebulizer pressure was regulated so that the cycling characteristics of the respirator were not altered and the IPPB as provided by the respirator was not hampered.

The nebulizer provides humidification of dry oxygen or other gases when IPPB is used for several hours or more. Pharyngeal irritation by dry gases has been previously reported⁸ as a limiting factor to prolonged application of IPPB in apneic patients or in those with respiratory depressions of various types. The use of dry gas for one hour or more may produce annoying throat irritation in some conscious patients. Humidifiers previously designed for use with IPPB apparatus have been bulky and cumbersome while the nebulizer is small, compact, portable and easy to operate. For prolonged IPPB in patients with or without spontaneous respirations water should be used in the nebulizer at frequent intervals unless there is some distinct contraindication to moisture such as pulmonary edema.

Twenty-six patients with silicosis, emphysema and dyspnea, with and without superimposed bronchial infections, have been treated by the IPPB nebulizer method. All patients received a course of treatment of one to two weeks' duration, consisting of four fifteen minute applications per day of IPPB using 100 per cent oxygen and 1.5 cc. of 0.5 per cent neosynephrine in the nebulizer. Secondary reactions have not been noted from the use of 1.5 cc. of 0.5 per cent neosynephrine administered in this manner. Use of penicillin in concentra-

* This apparatus is manufactured by the Mine Safety Appliance Co. (Pneophore was used for producing IPPB.)

tions as high as 50,000 units in 1.0 cc. of saline combined with the aforementioned amount of neosynephrine in patients with superimposed bronchial infection has been satisfactory. Both respirator and nebulizer should be cleaned after each treatment period, especially after using penicillin.

All patients treated thus far have reported some subjective relief consisting primarily of less "tightness" of the chest, "lighter" and easier breathing, decreased secretions and cough, improved appetite and more strength. Usually for the first two or three days after the beginning of treatment the amount of secretions has been increased and frequently, in the anthracite coal miner group, the sputum was black or dark-tinged even though the patient may not have been in a coal mine for several years. After about a week of treatment the secretions dwindled and in some cases totally disappeared. It is probable that the most beneficial effect from IPPB with a vasodilator agent in this group was the promotion of drainage of the bronchi and bronchioles. However, this combination therapy also provides an effective method of treatment during acute respiratory episodes in a group of patients with marked diminution of breathing reserve and with poor respiratory excursions. In silicotic patients the degree of emphysema as evaluated by x-ray is frequently most marked in the lung bases. Fluoroscopy has revealed increased ventilation in the lungs of all patients receiving IPPB, and this increase is especially noticeable at the lung bases in silicotic patients who had limitation of diaphragmatic movement. Pulmonary function studies were made on twenty-five of this series of patients before and after the course of IPPB nebulizer treatment. These studies, including maximal breathing capacity, vital capacity, minute ventilation and the estimation of emphysema (residual air expressed as per cent of total lung volume), showed no significant changes.

In three patients who had repeated attacks of asthma with intercurrent bronchitis, immediate relief was afforded by the

combined use of IPPB and neosynephrine or isuprel nebulization. One patient (a physician) reported that relief from the treatment was faster and more effective than epinephrine administered parenterally. The type of IPPB apparatus used here should not be used on a patient in a severe acute asthmatic attack because the instantaneous flow rate is not large enough;⁸ however, it can be used after the patient has been given sedatives or the acute attack has subsided.

SUMMARY

The use of IPPB with a nebulizer offers a method by which an aerosol can be distributed in the lungs more effectively in some patients than was usually possible by other technics. Fluoroscopy shows increased ventilation of the lungs, especially at the bases, with IPPB. Since IPPB increases the effective alveolar air, the value of vasodilator substances, chemotherapeutic and antibiotic agents thus administered in pulmonary disease would be enhanced. The combined use of the nebulizer containing an aqueous solution with IPPB apparatus tends to prevent irritation of the throat by the dry gas. In anthrasicotic patients with dyspnea promotion of better drainage from the bronchi and bronchioles appears to be the most beneficial effect of IPPB combined with a nebulized vasodilator agent.

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Psychosomatic Medicine*

Its History, Development and Teaching

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ONE of medicine's most challenging and necessary tasks today is to correlate the physical and emotional elements of illness, to erect a common ground on which the sciences of medicine and psychiatry may stand together not as contenders for the health of man but as equal partners in its service. No longer need physicians lead a "double life," reserving their confidence in organic diseases for those hours spent in the office or laboratory, but elsewhere living the life of anxious, apprehensive and fearful men. The Hyde, who in his office blandly tells his neurotic patient that there is nothing wrong with him, is a different man from the Jekyll of the home who worries about himself, his family and the future, whose discourses on politics and religion lack the cold scientific reasoning expressed in his consulting room. This divided allegiance between the organic and functional elements of disease is accepted by many who frankly believe that man must live in two worlds and that he should not mix his science with the emotions. Recent studies tend to refute this attitude as unscientific.

One who faces the hard facts of history today, however confident he may be, can hardly say that all is going well with Man. This has arisen from the fact that intellectual achievement as expressed in the progress of science is cumulative and thus has been able to outrun the mental qualities of man. These qualities being so closely involved with instinct and so near the purely biologic level are hard to change.¹

If one grants the vital necessity of bringing together the two disciplines of mind and body, psychiatry and internal medicine, how best can this be accomplished? Since this is a major task of education, we must look to the Universities to meet the problem. But in the meantime what to do for those physicians who are interested in this "new" concept, who wish to pursue and study it but who find no formal course open to them at this time? Many of the younger physicians have returned from military service with the realization that their training had been entirely too limited in scope.² Regardless of their specialties they soon discovered that a high percentage of their medical problems were psychosomatic, and because of lack of training in this field found themselves quite unprepared.

The object of this paper is to survey the development of psychosomatic medicine and to give the writer's experience in the teaching of this subject since 1936, and to present a bibliography which may help the physician in his reading on the subject.

HISTORY

While it is not novel anymore to say that the psychosomatic concept has been known for thousands of years, it is still interesting to record that Socrates over 2500 years chided the Athenian physicians for their organistic medical attitude. He expressed the view that the body could not be cured without treating the mind, that the cure of many diseases was unknown because physicians were ignorant of the whole.³ Aristotle

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went even further in suggesting that emotions are associated with physiologic responses and that these responses do not correspond in intensity to the emotion since some emotions are subconscious and therefore not evaluated.⁴ Thus from the days of the early philosophers, medical science and biology have been struggling to find an integrative formula, an approach which would offer both a methodologic unity and an empirical coherence to our clinical studies.⁵

It was the generation of German medicine in the middle of the nineteenth century which was particularly keen in its search for a new and more scientific understanding of medico-psychologic problems. Those concerned with psychosomatic medicine today owe a great deal to that generation, particularly to Nasse and Jacobi. Nasse sought not only to understand the relationship between mental illness and the physiologic economy but introduced an original note which is particularly familiar to the present day psychiatric clinician. He reported that any physical disease produces a disturbance in the relationship between the psyche and the soma. In 1838, Jacobi published a paper entitled "Further discussions of the foundation of somato-psychic medicine." This would seem to be the first medical formulation of the concept of the intent of psychosomatic medicine which is therefore over a century old.

However, these concepts were born at a time when medicine had fallen into the extremes of organic orientation. Medicine had become a natural science based on the application of the principles of physics and chemistry to the living organism. The laboratory approach disclosed an incredible collection of more or less disconnected details and this inevitably led to a loss of perspective. The traditional etiologic view was a localistic one based essentially on Virchow's brilliant concept of cellular pathology. The symptoms of the disease were now explained by morphologic changes in the organs. Pasteur's and Koch's discovery of pathogenic micro-organisms made

the infectious origin of the pathologic tissue changes the center of research. This one well defined mechanism soon became the model for all etiologic research. Other factors which had been discovered as causative agents, mechanical, thermic or chemical, followed similar principles.

The overpopularization of certain psychologic discoveries at the end of the nineteenth century had created a reaction against psychology and psychiatry by the medical profession. By way of the same reaction, it tended to become more somatologic. The reappearance of the term "psychosomatic medicine" and of the concept of the psychobiologic unity of the human being mark a renewed attempt to produce a synthesis of the total reactions of human personality. This process, started over a hundred years ago with less scientific equipment, had greater clinical intuition.

Few have understood the essence of this phase of medical development better than Gregg who wrote in 1936: "The totality that is the human being has been divided for study into parts and systems: one cannot deny the method but one is not obliged to remain satisfied with its results alone. What brings and keeps our several organs and numerous functions in harmony and federation? And what has medicine to say of the facile separation of the mind and body? What makes an individual what the name implies—not divided? The need for more knowledge here is of exasperating obviousness. But more than mere need, there is a foreshadowing of changes to come. Psychiatry is astir, neurophysiology is crescent, neurosurgery flourishes, and a star still hangs over the cradle of endocrinology. Contributions from the other fields are to seek from psychology, cultural anthropology, sociology, and philosophy as well as from chemistry, physics, and internal medicine to resolve the dichotomy of mind and body left us by Descartes."⁶

Since life itself is stronger than theories, the large number of sufferers who did not profit from the laboratory studies of scientists forced the medical profession by sheer

strength of numbers to re-evaluate the situation. The psychoneurotics who constitute probably the majority of all human sufferers wanted help. As a result one of the saddest anomalies of medical history developed. The physician whom these patients forced to listen to their psychologic complaints, who was unable to understand and to handle these symptoms with his one-sided training and equipment, began to dislike this type of neurotic patient. He refused to consider them as really sick and often accused them of malingering. In order to defend their scientific attitude, physicians had developed a distaste for psychologic facts and now they turned this distaste against their psychoneurotic patients. These patients were regarded as a nuisance and were considered a living accusation against the inadequacy of prevailing methods and dogmas. The physician became impatient with the nervous sufferer and stubbornly refused to deal with his symptoms on a psychologic level.

RÔLE OF MODERN PSYCHIATRY IN THE DEVELOPMENT OF MEDICINE

Psychiatry, as the study of the morbid personality, was to become the gateway for the introduction of the synthetic point of view into medicine. Advances in neurology paved the way for a more comprehensive understanding that in the last analysis all parts of the body, directly or indirectly, are connected with a central governing system and are under the control of this central organ. The central nervous system has both the function of the regulation of the internal vegetable processes of the organism and also the regulation of its external affairs, its relation to the environment. It is assumed that the complex neurophysiology of mood, instinct and intellect differs from other physiology in degree of complexity but not in quality. Whereas physiology approaches the functions of the central nervous system in terms of space and time, psychology approaches it in terms of those subjective phenomena which we call psychologic

and they are the subjective reflections of physiologic processes.

Recently more and more evidence is emerging that probably the functions of the ductless glands ultimately are also subject to the functions of the highest centers of the brain, that is to say the psychic life.⁷

The fact that the mind rules over the body, no matter how much it was neglected by biology and medicine, is the most fundamental fact which we observe continuously during all our life. Our body carries out most complicated and refined motor activity under the influence of such psychologic phenomena as ideas and wishes. All our emotions are expressed by physiologic processes; sorrow by weeping, amusement by laughter, shame by blushing, fear by palpitation, anger by increased heart activity, elevation of blood pressure and a change in the carbohydrate metabolism, and despair by sighing. Because these psychomotor processes belong to our normal life and have no ill effects, medicine until very recently paid little attention to their finer investigations. These changes in the body as reactions to acute emotions are of a passing nature. When the emotion disappears, the corresponding physiologic changes also disappear. The study of neurotic patients showed that under influence of more permanent disturbances chronic dysfunctions of the body develop. At first these chronic bodily changes were observed in hysterics. Emotionally conditioned disturbances of the internal vegetative organs which are not under voluntary control, such as the heart and stomach, have also been observed.

This has led to the concept of "organ neurosis" later called "somatization reactions" following the second World War. These are disturbances of the internal vegetative organs caused by nerve impulses, the ultimate origin of which are emotional processes most probably localized in the cortical and subcortical centers of the brain. Another term often used for these disturbances is "functional disturbances" since the tissues do not show any morphologic changes discernible by the microscope. In

such cases the anatomic structure of the organs is unchanged; only the co-ordination and the intensity of the organ function is disturbed. They are reversible. Since these functional disturbances are caused by emotional factors, psychotherapy thus gained a legitimate entrance into medicine proper and could no longer be restricted exclusively to the field of psychiatry. Since these emotional conflicts arise during the life of the patient in his relationship with other human beings, the patient as a personality became an object of therapy.

Psychogenic factors in disease mean the production of physical symptoms by the powerful biologic urges which motivate our lives, fear, hate, love and the forces which drive men and women to heights of accomplishment and heroism but also to the depths of despair, to neurosis or psychosis, to murder or to suicide. These motivations can best be understood by studying their manifestations in thought, phantasy, dreams and behavior. Under certain conditions, particularly the intensification of these drives without adequate expression, they can affect the physiology sufficiently to produce symptoms in the psychologic, the muscular or the vegetative spheres.⁸ More and more clinicians are beginning to suspect that functional disorders of long duration may lead slowly to genuine organic disorders based on visible anatomic changes. Thus the hyperactivity of the heart may lead to hypertrophy of the heart muscle; hysterical paralysis of a limb may lead, due to inactivity, to certain degenerative changes in the muscles.

This view of the causation of certain organic disorders means a remarkable change of traditional concepts. In these cases the pathologic-anatomic changes are secondary results of a disturbed function and the disturbed function itself is the result of chronic emotional conflicts. Thus, we have pathologic function as the cause of pathologic structure.

There is much evidence to show that just as the pathologic micro-organisms are specific and have a specific affinity to certain

organs so also the emotional conflicts are different from each other and are liable in accordance with these differences to afflict different internal organs. Inhibited rage seems to have a specific relationship to the cardiovascular system; dependent, help-seeking tendencies seem to have a specific relationship to the function of nutrition. Again, a different and specific conflict between sexual wishes and dependent tendencies appears to have a specific influence upon respiratory processes.

The increasing knowledge of the relations of the emotions to normal and disturbed function requires that for the modern physician, emotional conflicts should become just as real and tangible issues as visible micro-organisms. Menninger emphasizes this point more dramatically by saying that this knowledge will bring an awareness of man's daily struggles as having as much or more to do with the way he may feel as bacteria or bullets.⁹ He should be trained to use the psychologic microscope as he had been trained to use the optical microscope, a psychologic technique by which the emotional life of the patient can be subjected to detailed scrutiny.

This psychologic approach to the problems of life and disease brings the internal body processes into a synthetic unit with the individual's external relations to his social environment. It gives a scientific basis to such empirical everyday observations as that a patient often shows remarkable recovery if he is removed from his family environment,¹⁰ or if he interrupts his everyday occupation, and thus is relieved from those emotional conflicts which arise from family life or professional activity. The detailed knowledge of the relation of emotional life and body processes extends the function of the physician. The physical and mental care of the patient can again be united in one hand. The division of the healing profession between organic and functional disease has been an artificial one based on insufficient knowledge of the functions of the body and personality in their mutual interrelation.¹¹

PSYCHOSOMATIC INVESTIGATIONS

With the publication of the *Journal of Psychosomatic Medicine* in 1939¹² and the formation of the American Society for Research in Psychosomatic Problems in 1942,¹³ research in this field, both clinical and experimental, was accelerated and extended in scope.¹⁴ Various groups of investigators¹⁵⁻²⁰ working with animals were able to produce different types of psychosomatic responses. The physiologic expression of animals conditioned in such a way as to produce anxiety showed disturbances of gastrointestinal function in the form of diarrhea or constipation with a persistent loss of weight and an increased susceptibility to infection. More specific organ neurotic function may also occur such as pulse irregularities, pollakiuria, limping, incontinence, and premature ejaculation. Hudgins²¹ was able to produce highly individualized configuration of visceral reactions in a group of people. His subjects were able to contract their pupils by a particular mode of thinking. This was brought about by a conditioning process.

The literature on the clinical investigation of psychosomatic problems has become voluminous. Since the physical reactions to emotional disturbances may take on any form, for the convenience of description one may classify and discuss these reactions under four headings (at the end of the war the American Army used seven categories):²² (1) the gastrointestinal, (2) the cardiovascular, (3) the large group of aches and pains included in the category of headache, joint and muscle pains and (4) the allergies.

1. *Gastrointestinal.* Most clinicians are impressed with the emotional elements in peptic ulcer. Many²³⁻²⁸ consider it to be a psychosomatic disorder. This approach makes understandable observations which previously were difficult to integrate into the accepted concepts of peptic ulcer. The scientific literature on digestive malfunctions and its relationship to emotions has been covered by the exhaustive works of Dunbar,²⁹ Alexander³⁰ and Schilder.³¹

Many workers³²⁻³⁶ have noted recurrence of ulcer activity with the appearance of tension in the lives of ulcer patients. The character structure of the ulcer patient is such that when the proper stimulus presents itself he becomes embroiled in a conflict which produces tension. Alexander,³⁷ Mittleman and Wolff³⁸ and others have described the peptic ulcer conflict as developing from an unconscious longing for a dependent relationship and a reactive striving for assertive independence. Draper³⁹ describes his ulcer patients as forever striving to attain some goal notwithstanding difficulties which most men consider as insurmountable. By means of the electroencephalogram Rubin and Bowman,⁴⁰ taking the alpha index as a criterion of the passive personality, found a close relationship between peptic ulcer and a passive, receptive, fundamental personality structure.

Although the underlying conflict in the peptic ulcer patient appears to be the same, the outward appearance and attitudes vary considerably. Such differences depend upon the personality adjustments and defenses utilized and developed to solve interpersonal problems of which the ulcer conflict plays an important part. Thus the ulcer patient may appear to be talkative, taciturn, cheerful, sullen, belligerent, meek, cocky, bashful, misanthropic, amiable, hyperkinetic, sluggish, bright, dull, aggressive or unobstructive. It is therefore somewhat naive to believe that one can recognize the "ulcer type" by his appearance alone.⁴⁰

In 1932 Cushing²³ postulated that operation on cerebellar tumors results in disturbed balance of the components of the autonomic nervous system supplying the esophagus, stomach and duodenum and that emotions might effect a similar imbalance likewise resulting in ulceration. Wolf and Wolff,⁴¹ working on their subject Tom who had a gastric fistula, found during states of fear and depression a predominantly sympathetic stimulation resulting in gastric hyposecretion, hypomotility, mucosal pallor and decreased mucin production. Emotions of resentment, anger and anxiety

were found to be associated with hypersecretion of acid and pepsin, hypermotility, hyperemia and increased mucin elaboration, predominantly parasympathetic effects. When conflicts involving both fear and resentment existed, a dissociation response was observed frequently, resulting in hypersecretion of acid and pepsin and increased motility, but in this instance there was a *decrease* in mucin, a substance which ordinarily protects the mucosa from the erosive action of normal gastric juice. Such a conflict, then, results in physiologic changes that appear to be highly conducive to the development of erosion. Sustained emotional tension, productive of overstimulation of the stomach, can lead eventually to ulceration. Recurrent ulceration following subtotal gastrectomy may be explained partly by the conflict situation persisting or reappearing in the presence of sufficient remaining acid- and pepsin-bearing glandular tissue. Post-gastrectomy symptoms of weakness, tiredness, sweating, lassitude and procrastination form a not uncommon syndrome observed postoperatively in those patients whose conflicts have not been solved or who are unable to meet the problems of the moment adequately. This syndrome is seen most commonly in veterans.

Zane,⁴² van der Heide⁴³ and Eusterman²⁵ all conclude that peptic ulcer is a psychosomatic disease; that the causative factor which is operative in the vast majority of cases is the psyche mediated through the autonomic nervous system, thus engendering a morbid physiologic state conducive to the initiation, extension and chronicity of the lesion. This concept affords a better understanding of the many confusing manifestations of the ailment and makes available a more flexible and effective approach to them. As a gastro-enterologist, Sydney Portis believes there is need for a healthy cooperation in the pooling of somatic and psychologic knowledge; that then and only then will the patient get real service from the medical profession.⁴⁴

Similar studies have been made on cases of non-specific ulcerative colitis and it has been shown that many of these patients have character traits which cause them to react to certain external situations in a similar way. The onset or recurrence of the disease is preceded by an emotional trauma which produces a specific internal conflict, an acute love loss combined with humiliation. This makes these patients feel their inferiority as men or women.⁴⁵⁻⁴⁸

The clinical syndrome of anorexia nervosa and its attendant complexities has also been the subject of considerable study.^{49,50} Nearly all investigators emphasize the factor of the child-parent relationship, especially the relationship to the mother as the most important factor in the disease.⁵¹ The importance of the interaction of the environment and the personality organization of the patient has been outlined by Waller, Kaufman and Deutseh.⁵² This malady is characterized by depression of a wide range of functions: basal metabolic rate, temperature, estrogenic function, blood pressure, gastrointestinal muscular activity and its secretions. This psychosomatic disease behaves contrariwise in this respect to the other psychosomatic diseases in which there is exaggeration of one or more natural functions.⁵³

2. *Cardiovascular.* There are indications that emotional conflicts of another kind may cause continued fluctuations of the blood pressure which overtax the vascular system. Psychosomatic research in this field is not intended to be definitive but merely serves as a basis for further systematic studies which may lead eventually to an etiologically founded therapeutic procedure. Alexander^{54,55} came to the conclusion that the early fluctuating phase of essential hypertension is the manifestation of a psychoneurotic condition. This is based on excessive and inhibited hostile impulses. Extensive studies of the emotional lives of patients with hypertension have been published by Dunbar⁵⁶ and Wolfe.⁵⁷ They call attention to the increased tension and occasional spasm of voluntary or smooth

muscle, either or both of which may be alleviated as unconscious conflicts become conscious. They believe that this tension is part of the whole defense mechanism; psychologically and physiologically a general attitude of being on guard. Leon Saul⁵⁸ reports the finding of hostility in his series of cases. Katz and Leiter⁵⁹ state “. . . that numerous and various approaches to the problem of hypertension have been made and are still necessary to its solution. Not the least of these is the psychosomatic study of man in relation to his environment, internal and external alike.” Morris,⁶⁰ in a study carried out on student nurses and student pilots, found no correlation between changes in the pulse and blood pressure and instability. Instability instead of hostility or repressed resentment were looked for which may account for his conclusions. Hamilton⁶¹ investigated the psychophysiology of blood pressure in 373 young males with elevated blood pressure and found them as a group to tend toward less physical and social activity. They tended to move and walk more slowly and exhibited a definite tendency to avoid exercise and sports. They were somewhat less dominant and self-assertive. They had fewer friends and were somewhat more susceptible to anger. In a case of identical twin brothers, hypertension occurred in one and not in the other. The twins were of exactly opposite temperaments.⁵³

Binger, Ackerman, Cohn, Schroeder and Steele, in a monograph on Personality in Arterial Hypertension,⁶² came to the conclusion that “What appears to differentiate this from other neurotic disorders is the fact that after prolonged unresolved struggle between dependent strivings and compensatory aggressive drives, there is finally submission on the part of the patient to the hostility of the parent figure and acceptance of defeat of his own aggressive drives. When this occurs, anxiety, depression and temporary disorganization of the adaptive functions of the personality manifest themselves. Such acute emotional decompensations coincide with the discovery of hypertension.

The failure of the integrative functions of personality, the inadequacy of the characteristic defenses against anxiety, the inefficiency of the repressive mechanisms and the inability to develop an organized neurosis, rather than the nature of the underlying ‘instinctive’ drives, are what appear to differentiate this disorder from other seemingly similar ones. Although there may be a relationship between the disorder of the personality described and hypertension, the conclusion has not been drawn that one is the ‘cause’ of the other.”

Perhaps in no other system of the body is the iatrogenic factor as important as in the cardiovascular system. Functional disorders of the heart induced in the patient by the physician during his examination or by his manner of discussion of the patient's condition, occur more frequently than they should. Doubt in the patient's mind as to the integrity of the heart is a very frequent cause of chronic incapacity and a type of disability that is extremely difficult to alleviate in a neurotic patient.^{63,64}

3. *Headaches, Joint and Muscle Pains.* Patients with chronic headache present a considerable problem to the practitioner both because of their numbers and because of the stubbornness with which their symptoms often persist despite every effort of treatment. The great majority of all patients with chronic headache fall into one of three groups, migrainous, post-traumatic or psychogenic.

The psychogenic headache may be produced experimentally⁶⁵ by the intravenous injection of a small amount of histamine, that is, by stimulating the pain-sensitive structures in or near the walls of the large intracranial arteries by forcible vasodilatation. There is no definite evidence at present that this headache is caused by histamine sensitivity or by any other disorder of histamine metabolism.

Regardless of the precise mechanism of the production of pain, there is abundant clinical experience to prove that all three types of headaches are readily precipitated and made worse by emotional stress and

inner conflicts. As in the other conditions mentioned before in this paper, neither the psychologic nor the physical aspect of the headache can be neglected with impunity.

Alvarez,⁶⁶ H. G. Wolff,⁶⁷ Moersch,⁶⁸ Weber,⁶⁹ Touraine and Draper,⁷⁰ Knopf,⁷¹ Slight⁷² and Trowbridge and his co-workers⁷³ all investigated the migrainous personality and found these patients to be intelligent, hypersensitive, tense, worrisome, easily and suddenly fatigued, sensitive to smells, drafts and bright lights. They are usually politely obstinate and somewhat paranoid. Donald Ross and Francis McNaughton,⁷⁴ in their objective studies in migraine by means of the Rorschach method, found in these patients a persistence toward success, difficulty in sexual adjustment, perfectionism, inflexibility, conventionality and intolerance. Some of these are obsessive-compulsive features and all have been found in migraine by clinical personality study.

Dunbar⁷⁵ was one of the first investigators to describe the personality profile of sufferers from rheumatic disease. She divides these patients into two separate groups, one group with recurrent polyarthritis but with little or no cardiac damage and the second group with heart disease but with a history of only vague "growing pains." Time does not permit going into this fully and the reader is referred to Dunbar's description.

This type of patient attempts to please irrespective of whether the person to be pleased is superior or equal, male or female. The conflict to which he is subject makes his need to please especially acute.

In Scotland, Halliday^{76,77,78} found that patients with rheumatoid arthritis have an air of detachment and lack exteriorized tension. They show a quiet friendliness and a comparative absence of depression. In his opinion it remains to be seen whether further research will uncover a more specific rheumatoid personality type.

Toward this end, many workers⁷⁹⁻⁸⁵ have contributed important observations on the relationship of psychologic mechanisms. Seeking an understanding of physiologic mechanisms, other investiga-

tors⁸⁶⁻⁸⁸ studied the relationship between emotional reactions and skin temperatures in these arthritics. Johnson, Shapiro and Alexander⁸⁹ found that these patients express and discharge unconscious emotional tendencies through the voluntary muscles just as in hysterical conversion. They assume that these muscle spasms and increased muscle tonus may, under certain conditions, precipitate an arthritic attack. William Menninger⁹ reports that in the late war there were many cases of psychogenic disorders characterized by joint or musculoskeletal pain resembling myositis or fibrositis.

The occurrence of neurotic manifestations in and around the spinal column has been rather neglected by most medical men. Jones and Lovett⁹⁰ have discussed the features of the neurotic back symptoms quite thoroughly. Whitman⁹¹ distinguishes between the "neurotic spine" and the "hysterical spine." Wechsler⁹² includes certain back symptoms as examples of conversion hysteria. He comments upon the fact that pain in the back may be a common and persistent neurotic complaint. Neuralgias and myalgias of the back as types of organ neurosis have been described by many investigators.⁹³⁻⁹⁶ Saul⁹⁷ investigated the mechanism of psychogenic back pain and found that, like many other psychosomatic symptoms, it may result from an actual local physical condition which is exacerbated or possibly entirely caused by emotional tensions. Fetterman⁹⁸ advises that organic disease of the back be ruled out first because the symptoms in vertebral neurosis are no different from the complaints in organic disease. This self-evident statement applies to all types of functional disorders. However, the symptoms in the aggregate may give a clue to their psychic origin. Since psychogenic backaches are frequently organic at the outset, he describes clinical material often overlooked and gives certain points in differential diagnosis.

4. *Allergies.* The literature on psychogenic factors in asthma has been well summarized by Dunbar²⁹ and Wittkower.⁹⁹

In 1937 the Asthma Research Council in their "Report of Progress" for that year state: "Dr. Strauss has continued his investigations of the psychogenic factor in asthma and has concluded that psychic factors contribute to the asthma syndrome in even greater measure than had been thought likely."¹⁰⁰ In their "Report of Progress" for the next year on vasomotor rhinitis they found "that the psychologic element was of even greater importance than they had anticipated."¹⁰¹ Eyermann¹⁰² reports that those interested in allergy pay too little attention to the psyche and that those interested in the psychic conditioning of bronchial asthma are not aware of the possible allergic explanations for the vagaries of this disease. Karnosh¹⁰³ points out that no allergic person can be adequately evaluated without considering the personality structure in which the disease is implanted. Mitchell, Curran and Myers¹⁰⁴ found that the group of patients with negative skin-reactions are also the multiple complaint group. They express a variety of illnesses and complaints indicating a strong content of factors characteristic of psychologic maladjustment. Of fifty unselected cases of bronchial asthma taken from the allergy clinic by Neil McDermott and Stanley Cobb,¹⁰⁵ 72 per cent seemed to have an emotional component in their asthmatic attacks.

In the monograph on Psychogenic Factors in Bronchial Asthma, Thomas Franch¹⁰⁶ attempts to define the particular type of conflict commonly found in asthmatics. In summarizing the literature and findings, he states: "the impression gained is that attacks of bronchial asthma seem to be associated with very considerable variety of emotional conflicts. Outstanding among these are the suppression of any sort of intense emotion, threats to dependent relationships and to the security based upon them, and sexual conflicts. The outstanding personality traits of asthmatic children seem to be over-anxiety, lack of self-confidence and a clinging dependence on the parents which appears to be a reaction to a tendency to

over-solicitude upon the part of the parents." Using the Rorschach test and psychiatric examination, Viva Schatia¹⁰⁷ found asthmatics to have compulsive personalities without evidence of phobias or obsessions.

If the majority of asthmatics suffer from unsolved conflicts, it is a matter of interest then to find out the proportion of asthmatics among those who have supposedly "solved" their conflicts through a flight into psychosis. Leavitt,¹⁰⁸ investigating almost 12,000 patients suffering from functional psychosis in State Hospitals, found only ten cases of asthma. This is only about one-twentieth of the number of asthmatics found in the general population.¹⁰⁹ MacInnis¹¹⁰ in a survey of two mental hospitals each having 3,500 patients found only five cases of bronchial asthma in five years in one hospital and none was present in the other.

In the case of urticaria the rôle of psychologic factors has long been recognized. The literature on this subject has been reviewed by Dunbar,³ Fenichel,¹¹¹ and Sutton and Sutton.¹¹² Fenichel indicated that the tendency of the skin to be influenced by vasomotor reactions, which in turn are evoked by unconscious impulses, has to be understood from the point of view of the general physiologic functions of the skin. It displays four characteristics whereby it represents a boundary between the organism and the external world. (1) In its protective function, the skin treats internal like external stimuli and uses vasomotor functions as an armour. (2) The skin is an important erogenous zone. In addition to the stimuli of touch and temperature pain, too, may be the source of erogenous cutaneous pleasures. (3) Being visible, the skin is a site for expressions of conflicts around exhibitionism. These conflicts concern not only fear and shame but also various narcissistic needs for reassurance. (4) Anxiety is physiologically a sympathicotonic state, and sympathicotonic reactions of vessels in the skin may represent anxiety. It is well recognized that the skin may react to normal emotional situations by flushing, pallor or sweating, and that the degree of

this reaction depends upon the individual. Davis and Bick¹¹³ suggest that in the same manner anxiety is a quantitative exaggeration of a mild tension of nervousness. Therefore, some forms of dermatitis are quantitative exaggerations of mild skin reactions. This is an additional symptom of an anxiety state occurring in a sensitive individual whose anxiety is reflected through the skin rather than through the gastrointestinal tract or cardiovascular system.

People can be just as sensitive to certain ideas or situations as others to pollens. Menninger and Kemp¹¹⁴ report a case of urticaria in a young man caused by his inability to "be a man" in a love affair. Saul and Bernstein¹¹⁵ suggest the possibility of a relationship between certain states of allergic sensitivity and states of intense frustrated longing. There are certain differences between acute and chronic urticaria. Chief of these is the fact that while specific allergens are usually found to cause acute urticarias, it is exceptional to find this etiology in chronic cases. In the latter there are a great variety of factors operative, among them the psychologic and endocrinological.¹¹⁶ Kaywin¹¹⁷ came to the conclusion that his patients with chronic urticarias were shy, easily embarrassed, prone to blushing, relative passive-dependent and immature, with, perhaps, a tendency toward exhibitionism.

As a dermatologist and allergist, Sulzberger is skeptical of the psychologic factor. He states: "Psychic and emotional influences can perhaps elicit urticarial attacks and in many ways perhaps even favor the creation of allergic states and the elicitation of allergic reactions. I have never had the opportunity to observe purely psychogenic urticarial attacks, but their existence is reported by many careful observers such as J. Jadassohn, Sack and others in Europe and, in America, Stokes, Pillsbury, Kulchar and co-workers, in articles which merit careful reading by all interested in the problems of psychogenic and emotional effects in various dermatoses."¹¹⁸

Thus, in reviewing these four arbitrary

groups of psychosomatic problems, only a rabid psychosomaticist would insist that the impact of a persistent emotional situation upon a certain temperament is the whole story in the creation of such diseases. Obviously, there must be other mechanisms that we are as yet unaware of; physical, endocrine, humoral, etc. We must also consider that psychosomatic diseases possess a long life cycle and that the incubation period may be of many years' duration. Unfortunately our methods of approach are still crude and the interrelation between the autonomic, the somatic nervous system and the endocrine organisms are so close and so complex that it is difficult to isolate the reactions between the various systems.

It becomes apparent that it is not only the variety of emotion which is important but the way in which these emotions are experienced. One individual trembles, the second vomits, the third gets palpitation, the fourth gets increased peristalsis, the fifth flushes, the sixth pants for breath, the seventh feels a lump in his stomach; and these symptoms are reflected in physical expressions such as changes in blood pressure, increase or suppression in gastric secretion, increase in blood sugar, increase in intestinal secretion and tachycardia.

The diagnosis of these diseases depends upon a perspective of the composite picture in which a study of the personality and life history of the individual is a vital consideration. The life history should include a panoramic survey of the patient's life, his reactions to members of his family, his social and economic status, his loves, his fears, his strivings and his hates in a tridimensional history. The psyche and the soma of the patient should be viewed stereoscopically.

In this development of a psychosomatic disease there are five phases: (1) The constitution of the patient; (2) the exaggeration of a normal function; (3) the lability of the exaggerated function; (4) the fixation of this exaggerated function and (5) somatic changes.

It is in the transition between the fixation stage and the somatic changes, that is, the

elucidation of the mechanisms whereby fixed exaggerated function results in organic changes that one of the main problems in psychosomatic medicine lies. Usually by the time the somatic changes are crystallized the personality changes are also crystallized.

Psychotherapy to be effective must take place in the first three phases. It is of less avail in the fixed and especially in the somatic phase. In the last two phases, surgery has done much to reduce the exaggerated function to a lower level (sympathectomy, vagotomy, gastrectomy and thyroidectomy). However, in such fixed psychosomatic disease psychotherapy begins when the operation is finished.⁵³

TEACHING PSYCHOSOMATIC MEDICINE

Whether psychosomatic medicine, in its revival as an attempt to integrate psychopathology with heretofore isolationist biology and physiology, is to be considered a new specialty or a new form of medicine is a question that only the future can decide. At the present time there are two somewhat incompatible connotations of the term. In the opinion of the American Society for the Study of Psychosomatic Problems (soon to be called The American Psychosomatic Society) psychosomatic medicine refers only to a point of view. This is a psychologic orientation to all disease. In this concept it is a guiding principle of medicine which should apply to all illnesses and should represent the view of the surgeon and internist as well as that of the psychiatrist.¹² From this point of view the term "psychosomatic medicine" is a punitive one intended to reorientate medical thought from localistic thinking. If in years to come this orientation is accomplished, no doubt the term itself will be dropped as physicians learn to use this approach naturally.

There are others such as Halliday⁷⁸ for whom the term "psychosomatic medicine" is used to describe certain diseases. In his opinion the concept of a psychosomatic affection in its developed form brings into relationship a large number of seemingly unrelated facts. The outlook gained shows

that many "localized diseases," the names of which have been found scattered throughout textbooks of medicine under the headings of the various anatomic systems, may now be grouped under a unifying etiologic category. The term psychosomatic affection is therefore a valid symbol which provides a new instrument for thinking, for investigation and for the direction of action. In his opinion the psychosomatic affections comprise many of the chronic recurring forms of sickness and they incapacitate rather than kill.

These two divergent concepts serve to reflect the many confusions inherent in the change of traditional concepts of disease. Those interested in psychosomatic medicine today are thinking in terms of the necessity for the organism to maintain a homeostatic equilibrium within itself and within its environment. In the science and the practice of medicine there is a need for a new approach to classification based on psychosomatic concepts. Here the major contributions have come from physiologists on the one hand and from medical psychologists on the other. But it has been difficult to bridge the gulf between these two disciplines. Existing nosology is inadequate in both psychiatric and somatic aspects. The disease entities now recognized in each of these fields have little relevance to the organism as a whole or to the "organism-environment continuum." These are essential concepts in the psychosomatic approach. Psychosomatic disorders are not entities that can be catalogued under the earlier diagnostic labels invented by psychiatry or internal medicine or a combination of the two.

What is needed is a system of classification which will aim not at defining disease entities in the traditional sense but rather at describing dynamic processes in ill persons. It should begin with the organism-environment continuum, and its material should relate to the flow of energy in a field of tension. Illness in the biologic sense represents a failure of the organism's adaptability. The availability and lability

of the defensive mechanisms are of the utmost importance in influencing the clinical course and the therapeutic possibilities. To verbalize these conditions requires new medical nosology and the aid of general semantics.

In the present state of knowledge methods are not yet available to test the question of causation in the dynamic relationship of "psyche" and "soma." In Dunbar's opinion we are seriously in need of more clinical studies to trace the sequence of events in both spheres and of more experimental studies relative to the physiologic and psychologic components to clarify the problems of pathogenesis. The causality in disease constitutes a chain of circumstances and events and is never a simple and isolated factor.

In view of these difficulties it is not surprising that even with the present-day knowledge of psychosomatic medicine there is still far too wide a gap between the use of the word psychosomatic (and sometimes its glib use) and the deep understanding of what it really means and its therapeutic implications. What has been gained, however, is the acceptance of the psychosomatic approach by the medical profession though there are still many who are not even receptive to the ideas underlying this concept. Psychosomatic medicine no longer needs an apology.^{119,120} It has passed that stage. One may consider this acceptance as the first phase of the problem. The second phase, upon which we are now entering, consists of the task of teaching this new discipline to students and to those physicians who are interested in reorientating themselves to medicine. The study of psychosomatic medicine is largely in the hands of the youth of our profession.

As mentioned at the outset, this is a major task of education and we must look to the universities to meet the problem. In the meanwhile there are many graduates interested in learning this point of view and the literature in clinical journals aims to satisfy this need.¹²¹⁻¹³¹ That they do not satisfy this need fully is due in part to the

fact that not enough physicians are trained in the basic sciences of this new approach. Just as one would not expect to make an adequate medical diagnosis without first having been trained in anatomy, physiology, chemistry, pathology, medicine, etc., so one can hardly expect the physician to understand the psychosomatic approach without first learning the broad patterns of human motivation and personality development, its adaptations and its maladaptations. He must be able to recognize anxiety in its many forms of expression and he must be as familiar with the neuroses as he is with bacteria. Without this knowledge his study and reading of psychosomatic literature cannot but be confusing.

In the writer's opinion it is very difficult if at all possible to teach the psychosomatic approach to those whose "orthodox" training and orientation has become "fixed." To them, physicians who seem to have gained some insight into psychologic phenomena are either disregarded on the whole or relegated to the group of more or less queer doctors who have wandered off into philosophy. In attempting to teach the psychosomatic approach in the early nineteen thirties, the writer found himself in the unfortunate position of being considered an internist by the psychiatrists and a psychiatrist by the internists.

On the other hand, medical and pre-medical students absorb these teachings with avidity. Theoretically, the average student knows that there is a relationship between the soma and the psyche, but, actually he has relatively little conviction of the reality of this relationship. Following a series of lectures on psychosomatic problems given by the writer over a period of years to the McGill Psychological, Pre-medical and Medical Undergraduate Societies, a group of senior medical students, resident physicians and young practicing physicians was formed to study the subject of psychosomatic medicine. Classes were started in the writer's office and met twice weekly. These sessions lasted from three to four hours each and extended through the

winter seasons. By 1938 the class consisted of fifteen members.

In the beginning the instruction was very informal, haphazard and left much to be desired. At this stage the lack of organization was made up for by the enthusiasm of the group. Later, however, the course took on a more systematized and graded form. At the outset the patient-physician relationship was discussed. Physicians have two kinds of relationships with their patients. The first, and the one best understood, is the reality relationship. The second is a symbolic one in which the physician plays a psychologic rôle which is not altogether determined by reality. Here the emotional attitudes of the patient are based on earlier experiences. He may identify the physician with earlier figures such as the father or mother who have played an important rôle in the early life of the patient. This may produce a positive or negative transference.¹³⁵ The physician must be aware of it for a great deal of his success in therapy will depend upon the way he handles these attitudes. The physician on his own part may also develop certain emotional reactions toward the patient, countertransference and hostility are not infrequent and must be avoided if possible. The therapeutic values inherent in the patient-physician relationship are considerable and should be developed fully.^{132, 133, 134}

The next step was to study the normal development of the personality.¹³⁴ One of the most important attitudes in infancy and childhood is dependence. This dependency for food, shelter and protection is easily seen but the emotional aspects of this situation are much more subtle. The interrelationship of these two sets of factors, the practical things the child needs for survival and the emotional constellations centered around his biologic needs are crucial in the development of his personality. How these emotional needs are satisfied or denied predicates certain types of behavior upon which later neurotic symptomatology is based.

At first the infant's dependency mani-

festes itself in a somatic way through the gastrointestinal tract (oral and anal needs). When these needs are not met adequately, thumb-sucking or constipation may result. As the child becomes older the zones of intense interest shift. By three and one-half to four years of age the genital and urinary zones become the foci of interest not only in himself but in those about him, usually his father and mother. It is a period of intense activity and he learns to give up his socially unacceptable impulses by the age of five. This is the period of "thou-shalt-not" and the child begins to identify himself with the person who is advancing the "thou-shalt-nots." This is the age of nightmares, mild phobias and inner turmoil. By six he is ready to meet the world in terms of ideas instead of soma; he is ready to be taught. There is a decline in the child's emotional activity and the beginning formulation of conscience.

All these childhood dependency relationships are reactivated when a patient becomes ill and accounts for the childish dependency some patients have for their doctors—the basis of the doctor-patient relationship.

At this stage of instruction the technical terms of "id," "ego" and "super-ego" were explored and correlated with the child's development.¹³⁵ During the "latency period" from about six to twelve there is a tendency for strong identifications with important people in his milieu. He resolves this identification after puberty by denying and rejecting everything there is about the person previously identified with. He is unwilling to be passive any longer and now identifies himself with and wants to be like all the other boys in his group. This is a period of intense attachment to his friends. Sexual development in all its complexities in regard to his training now takes place and the period of anxiety, tension, guilt, moodiness, insomnia and anorexia are observed.¹³⁷ These neurotic symptoms during adolescence may be considered normal though ten years later these same symptoms would have the significance of a malignant psychologic process. There is a continuous

conflict between powerful forces in the individual, perhaps never so powerful as during puberty, for the pleasure-seeking self is eternal and relentless. This is the time he identifies himself with the coach of the sport he is interested in. If his repressions are strong, he may turn toward the religious side and identify himself with the priest or minister, the Y.M.C.A. leader or some other group leader. This helps him weather the storms of puberty. It is at this time that he is capable of great esthetic and idealistic striving. It is at this period that he makes great plans for the future. The end of adolescence differs with each individual. Some become mature early in life while others never give up some of their adolescent attitudes and activities.¹³⁶

The boy who comes through this adolescent period successfully settles down and feels reasonably certain of his ability to handle himself, his environment and his destiny. He leaves behind him his dependency on others and tries to remove his identification with figures of authority who dominated him in the past. It requires no great imagination to visualize the effects of important forces and counterforces which occur during this period of life and the damage they may do to the growing personality. This damage results in psychopathology.

The next object of study was the response of the individual to anxiety.¹³⁸ Each person handles anxiety in a different way. Many illnesses represent his way of dealing with it, his defense against the discomfort of anxiety or his translation of anxiety into a different area. When anxiety is expressed directly, he experiences it with all the physiologic and somatic discomfort implied in a sense of impending disaster. It is expressed through the cardiovascular apparatus in terms of palpitation, irregularities of rhythm, precordial discomfort, dyspnea and a sense of choking in the throat. If these somatic symptoms occur suddenly, as in an accident, the cause and effect are so obvious that the individual accepts these discomforts as a natural result of the experience. But should this anxiety be chronic and

prolonged, he might interpret them in his own mind as the result of some organic disease of his heart or stomach.

Not all individuals, however, handle anxiety directly. He may "blot" out the anxiety experience from conscious recognition and develop a substitute for it, such as hysterical reactions. Or he may mediate this anxiety directly through organs and somatic functions, as in psychosomatic disturbances. In these cases the anxiety is mediated through the autonomic nervous system and is translated into functional disorders of various organs or parts. The fluctuations in severity of the symptoms at first run parallel with the fluctuations of anxiety. Later these dysfunctions may become irreversible. Or, anxiety may become focused on certain experiences such as fear of high places, closed places, animals, dirt, insanity, syphilis, pregnancy or cancer. Then again, anxiety may be thinly disguised and lead to obsessive thinking or compulsive activities, or it may be disowned and projected into others in terms of suspicion and distrust. When anxiety is expressed indirectly, the anxiety itself is never recognized by the patient as such, only the symptom formation. The sources of his anxiety are unconscious. It is of importance to note here that similar psychosomatic responses may result from fear, anger and resentment; and in the same way these emotions may remain unconscious and only the direct symptoms may make themselves known.

Just as medical students are taught the technic of blood counts, sedimentation rates, urine analysis, blood sugars, etc., so must the student of psychosomatic medicine learn various psychologic tests¹³⁹ which help to evaluate the intelligence and the dynamic forces at work in the production of symptoms. The class was instructed in the use of the following tests:

1. Word Association Test¹⁴⁰⁻¹⁴⁴
2. Thematic Apperception Test¹⁴⁵⁻¹⁵²
3. The Wechsler-Bellevue Intelligence Scale^{139, 153}
4. The Minnesota Multiphasic Personality Inventory Test¹⁵⁴

5. The Picture Analysis Test¹⁵⁵

Just as complicated and specialized medical tests (such as hormone assays or x-ray examinations) are referred to specialists, so must some psychologic tests be left for those specially trained. Thus the important Rorschach Test¹⁵⁶ was described briefly and an outline for its uses given so that it could be requisitioned when necessary. Just as the urine and stool excreta are examined to evaluate bodily functions, so are the mental excreta, the dreams, examined to evaluate emotional drives. While it is inadvisable for the physician inexperienced in the study of dreams to interpret them to the patient, still, with a little interest and study he can often glean, simply from the topics of the dreams, what is central in the patient's mind: hostility, anxiety, desires for ease or escape, the pressure toward work and accomplishment, needs for superiority, etc.

Up to this time instruction was purely theoretic.¹⁵⁷ It now became necessary to demonstrate clinical material. As a first step, the cases seen in the writer's office that day were discussed much as ordinary case reports are reviewed at clinical conferences, with this exception: The class was asked to try to obtain more information from the instructor than was given them in the case report itself.⁴⁵ The main complaints and a very short history and physical examination were reported and they were asked how to proceed from there on; what important direction of probing was suggested by the type of history given and what form of therapy was to be instituted. As soon as the class showed a true grasp of the general nature of the psychosomatic problems dealt with in every day practice, live clinical material was presented.

Since the classes were held in the evening, clinic and ward patients were unavailable for teaching purposes. Because of this and because it had many advantages, hypnosis was used to produce manageable models of almost all types of psychosomatic problems.¹⁵⁸⁻¹⁶⁵ Hypnosis is one of the few experimental technics applicable to human

beings whereby it is possible to produce major changes in the organization of behavior. Without discomfort or danger to the subject,¹⁶⁶ extensive alteration in the pattern of experience which constitutes the self, and in those controls of behavior which we know as volition, are altered. It is possible to produce artificially and temporarily the diverse symptoms of hysteria¹⁶⁷ or with equal ease to make a manageable model of compulsive or obsessive neurosis.¹⁶⁸ By the same means artificial "complexes"¹⁶⁹ are induced and made effectively subconscious. The class was then able to observe, under controlled conditions, with known antecedents, the eruption of unconscious strivings into the normal stream of behavior and the methods of defense set up against them. Anxiety, rage, fear, frustration and other emotions and situations were suggested to the subject and made subconscious by suggestion. The resulting somatic manifestations were observed and studied. These phenomena became a reality and the constant interplay between psyche and soma was observable from moment to moment.

While in actual patients some of the conditions demonstrated would take many years to develop, in this type of demonstration technic the whole "life cycle" was carried out in the space of an hour or so. In order to integrate these observations into the student's general training the somatic manifestations in these demonstrations were measured and visualized by means of the sphygmomanometer, respiratory tracings using the basal metabolism machine,^{186,187,188} fluoroscopy of the stomach, heart and lungs, electrocardiograms, etc. For brevity, these hypnotic phenomena are listed below under general headings.¹⁶⁴

1. Altered Visual Behavior¹⁷⁰

- (a) Decrease in visual acuity with blurring of vision
- (b) Contraction of the visual field
- (c) Difficulty in focusing gaze
- (d) Decreased ability in depth and distance perception
- (e) Subjective sense of color vision

2. Altered Auditory Behavior^{171,172}
 - (a) Decrease in acuity
 - (b) Inaccuracy in localizing sound
 - (c) Distortion of perception of sound qualities
3. Altered Motor Behavior^{173,174,175}
 - (a) General muscular incoordination
 - (b) Specific motor disturbances such as paresis and paralysis, apraxias, speech disturbances, dysmetria, ocular fixation, pupillary dilation and nystagmoid movements
4. Other Types of Altered Behaviour
 - (a) Analgesias and anesthesia¹⁷⁶⁻¹⁷⁹
 - (b) Subjective reactions of nausea and vertigo¹⁶⁵
 - (c) Anxiety states and phobic reactions with their various physiologic concomitants¹⁶⁸
 - (d) Amnesias¹⁸⁰
 - (e) Revival of forgotten patterns of behavior¹⁸¹

At this stage of instruction all members of the class were taught the technic of hypnosis¹⁸²⁻¹⁸⁵ and the indications for its use. The history of hypnosis in medicine was reviewed and the subject matter placed in its true frame of reference. The "thumbnail" description of the history of hypnosis by White of Harvard University is worth repeating here.¹⁸⁹ "Hypnotism was branded with the scarlet letter by a commission of scientists who dismissed Mesmer's findings on the ground that the phenomena, though real, were the result of imagination, hence not of the physical stuff with which science could safely deal with at that time. Ejected from the better consulting rooms, hypnosis was destined to wander for a hundred years in the slums of medical practice, from which disgrace she was not rescued until the eminent neurologist, Charcot, picked her out of the gutter, examined her reflexes, and pronounced her worthy of a place in medical research. More recently, through similar good offices by Hull of Yale University, she has been allowed to enter the portals of experimental psychology, where in the past twenty years she has begun to live down her reputation, learn the manners

of the laboratory, and speak the language of polite science. Yet so recent is her social ascent that even in contemporary studies of hypnotism, there occasionally seems to linger the atmosphere of magic and darkened rooms rather than the clear light of reason."

Narcoanalysis and narcosynthesis, used during the war and since, is only a long recognized atypical form of hypnosis.^{190,191,192} Instead of the term "hypnotism" the use of such terms as hypnoanalysis, hypnotherapy and hypnosynthesis has aided the acceptance of hypnosis by the medical profession.^{183,193,194,195} It is now being taught in many of the best medical schools as a prerequisite subject in the post-graduate course in psychiatry.

The last topic for discussion in the course was psychotherapy.^{122,196,197,198} This represents one of the chief interests of the student and physician. The limitations of psychotherapy as well as its possibilities were constantly kept in mind. Emphasis was placed upon the avoidance of two attitudes commonly observed in relation to this problem, a more or less complete rejection of, or a too enthusiastic acceptance of the "psychologic" in medicine. The wisest psychology will never replace penicillin or the need for an appendectomy. The various forms of psychotherapy were evaluated. The rôle of reassurance, supportive therapy and other anxiety-allaying techniques were discussed. The differences in aim between these therapies and the so-called "anxiety-provoking" or "uncovering" psychotherapies were discussed in some detail. Insulin and electroconvulsive therapies,¹⁹⁹ adrenalin desensitization,²⁰⁰ narcoanalysis, narcosynthesis and hypnotherapy were reviewed. An attempt was made to help them recognize the more malignant emotional conditions so that they might be referred to specialists in that field. The use of empathy instead of sympathy in therapy was stressed. It was also emphasized that some psychoneurotic patients can never be completely well and that they must return from time to time to the physician for support and

guidance much as the diabetic and pernicious anemia patients remain under the supervision of the internist.

During the early part of the course members of the class became aware of the considerable tension with which some of their prejudices were charged. It was difficult at first for them to see the emotional and organic elements in illness stereoscopically. There is still a trace of the dichotomy of mind and body in the use of the term "psychosomatic" and the student is apt to separate instead of integrate the components of the disease. The ability to see illness as a dynamic, constantly changing adaptation to the stresses and strains, internal and external, to which the patient is exposed requires considerable effort and training. Obviously, this type of training should begin in the preclinical years.

To see what could be done for the general practitioner, an experimental graduate course was given in 1946 to twenty-five general practitioners of all ages to determine whether these men can be taught to practice in their offices the kind of medicine psychoneurotic patients need. This course was sponsored jointly by the Commonwealth Fund and the Division of Postgraduate Education of the University of Minnesota.^{134,201,202} Two weeks were considered adequate without depriving the busy physician of too much of his time. The teaching staff was drawn from the ranks of younger psychiatrists and somewhat older internists. Instruction was both didactic and clinical. Careful analysis by both students and instructors at the end of the course furnished evidence that this type of graduate education had been valuable in a practical sense.

A discussion on "The necessity for reorientation in medical education from the psychosomatic point of view" held in the summer of 1947 under the auspices of the American Society for Research in Psychosomatic Problems, revealed how complex and difficult this undertaking is at the present time. Many leaders in medical education took part in this discussion and

it was believed by several that such a reorientation must await the time when those who guide the medical faculties see for themselves the need for this type of training.

At the present time there is much to be said for the suggestion made by the Canadian Association of Medical Students²⁰³ and approved of in principle by the Editors of the *Canadian Medical Association Journal*²⁰⁴ for apprenticeship to a physician as a method of teaching. This holds true especially in the field of psychosomatic medicine where clinical training is essential.

SUMMARY

The need for a psychosomatic approach to the problems of medicine has been recognized for more than two thousand years. The reasons for the lack of progress in this field are given. The recent growing interest and research in psychosomatic medicine has resulted from the realization that many illnesses treated by the physician cannot be understood from an organic point of view alone. The steps by which psychiatry has become integrated into medicine itself are delineated. Research work done on psychosomatic problems is reviewed. The results of this research have led to the acceptance by the medical profession of the psychosomatic attitude, namely, not to study the soma less but to study the psyche more.

To make the medical profession aware of the need for a psychosomatic attitude toward medical problems may be considered to be the first phase of the question. The second phase, upon which we are now embarking, consists of the task of teaching this subject to medical students and to those physicians who have graduated since the advent of the last war.

A brief outline of the writer's method of teaching psychosomatic medicine since 1936 is presented.

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Seminars on Protein Hydrolysates

Assessment of Knowledge Concerning the Clinical Use of Protein Hydrolysates and Pure Amino Acid Mixtures*

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IN this series of seminars† the primary intention has been to evaluate the use of protein hydrolysates for clinical purposes. It is convenient to comment on the fresh light they shed on (1) the physiology and pathology of protein metabolism and (2) the therapeutic and nutritional advantages of protein hydrolysates and other amino acid mixtures.

PHYSIOLOGY AND PATHOLOGY OF PROTEIN METABOLISM

Peters opens the series with an able and concise survey of the effect of injury and disease on nitrogen metabolism, first indicating the factors which influence the amount of nitrogen stored or retained in the body at any one time and then discussing the effects of protein restriction, starvation and work. He has wisely stressed that the optimum proportions of the amino acids for growth and maintenance have been only roughly ascertained. Like the growing animal the protein-depleted animal can apparently use a great deal of dietary protein.

It is important to note that although a sustained positive nitrogen balance is accepted as proof of previous protein depletion, failure to establish a positive balance certainly does not exclude antecedent protein depletion. This failure may be due to insufficient energy or to a protein intake

deficient in quantity and quality. Dissociation in time of feeding of one essential amino acid from its fellows will prevent optimal use being made of the whole mixture.¹ Failure to achieve a positive balance may also be due to the catabolic response to injury, e.g., acute haemorrhage, operations and injuries, or to what has been called the 'toxic destruction of protein' associated with acute febrile illnesses.

Peters traces clearly the lack of success in preventing such losses of body nitrogen in the acute catabolic phase after trauma even when diets are administered which should be adequate in protein and far in excess of the energy needs of the patients. Peters finds that the amount of protein destroyed seems to vary with the severity of the injury or disease if the term 'severity' is loosely defined. This is in agreement with the present writer's experience.²

There is now a mass of evidence that a negative nitrogen balance of considerable degree almost always follows major accidental injuries although curiously the nitrogen loss after osteotomies is much less than after accidental fracture of the same bones, and a nitrogen balance can be made positive without difficulty after the repair of inguinal hernias but not so readily after appendicectomies.

Peters notes that the continued negative nitrogen balance after an acute illness often continues despite high protein diets and persists even after the temperature is normal

† These seminars may be found at the end of the references on page 890.

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and symptoms and signs of the illness have disappeared. In this case the losses of nitrogen seem to be related to the inherent gravity of the disease and not to its clinical manifestations. As the present writer³ pointed out the degree of fever following injury—traumatic fever—is so slight that we cannot hold fever responsible for the marked wastage of protein which may occur after an injury such as a fracture. Further, disuse atrophy is not the major cause of the loss that follows injury.^{3,4}

Strangely enough none of the papers refers to the remarkable parallelism in the behaviour of sulphur and nitrogen during the increased protein catabolism after serious trauma. The present writer drew attention to this many years ago.⁶ Incidentally, in the light shed by the brilliant work of Schoenheimer and his colleagues in which it was shown that the distinct streams of exogenous and endogenous streams of metabolism postulated by Folin were in reality inextricably mixed, it is sometimes forgotten that it was the catabolic reaction to injury which demonstrated that urea was as much a product of endogenous metabolism under these circumstances as was creatinine.

Munro and Cuthbertson⁷ showed that there is no increased loss of nitrogen after fracture of the long bone of a rat depleted of protein by being fed for some time on a protein-free diet. Evidence from the human field bears this out and indicates that protein is used in this profligate manner after injury only by previously healthy persons, and that after the height of the catabolic phase the loss of nitrogen gradually diminishes and, if an adequate diet is supplied, a positive nitrogen balance can be attained.

Just as Shaffer and Coleman⁸ were unable to prevent a negative nitrogen balance during the early stages of typhoid fever, although able to mitigate the loss by increased intake of energy, so the writer⁹ was also generally unable to attain nitrogen balance at the height of the catabolic phase following a severe injury. In this connection it is of interest that Browne and his associates¹⁰ found that during the period of posi-

tive nitrogen balance which succeeds the negative or catabolic phase renewed injury causes little waste of nitrogen.

Peters points out that attempts to prevent nitrogen loss in the early days of a fever, such as typhoid, were carried through with diets containing quantities of protein which, although considered high in those days, are not by present standards really so very high. Anorexia was the factor which prevented large quantities being ingested. The problem of feeding such patients has been reopened by the development of intravenous forms of alimentation. But despite all modern aids Grossman et al.,¹¹ Howard et al.^{12,13} and Browne et al.¹⁰ were unable to establish nitrogen equilibrium even with large amounts of protein diets high in energy value in patients with severe, acute infections or after serious injuries or operations.

The significance of positive results achieved by some tends to break down when the cases are studied in detail. The apparent success of Mulholland, Co Tui et al.¹⁴ in achieving a positive nitrogen balance in patients with gastrectomy by means of protein hydrolysates may have been due to the fact that these operations were performed chiefly on chronically wasted patients. Studies of persons with large exudative lesions, e.g., burns, must also be rejected for balance purposes unless the quantities of nitrogen lost in the exudates have been measured.

Peters suggests that the increase in nitrogen loss may be more apparent than real as it may be related to the protein intake only which is minimal immediately after an operation or severe injury. This is not in accord with the present writer's experience with fractures although he would agree with the view that injury appears to provoke no malicious destruction of protein but acts simply to compel the expenditure of a certain amount of tissue protein. Upon many occasions the writer has pointed out his belief that this catabolism of protein is part of a primitive reflex related to the need for energy and new materials by the injured animal which cannot search for its food.

The strange thing is that even when food is available during this period, the organism appears to make little use of it being, in general, geared to a catabolic or at least anti-anabolic phase. During this period an increase in energy intake does mitigate the loss to some extent. Elsewhere reference has been made by the writer² to the fact that anabolic activity may be going on but that this is masked by a more general catabolic effect. It is debatable if the administration of extremely large quantities of protein and a diet high in calories can spare native protein and it may be unwise to try to correct it. Indeed, there may be no special advantage in trying to correct this primitive catabolic reflex for, as Peters points out, Hirschfeld et al.¹⁵ found that the early administration of large amounts of protein to burned patients provoked diarrhoea and other untoward symptoms. In any case, previously healthy patients are soon able to take large quantities of food and thereby protect and restore their tissue losses.

One cannot really go much further than agree with Peters' statement that there is an impression that high protein diets improve the sense of well being and hasten the appearance of the anabolic phase, and that the patient who incurs an acute injury while in a state of debilitation deserves a high protein and energy rich diet from the start because he can use protein efficiently.

It should be noted that the work of Croft and R. A. Peters¹⁶ on the nitrogen-saving effect of methionine in burned rats, which is referred to by J. P. Peters, has not been confirmed by the senior of these two workers and his later colleagues.¹⁷ Further, Sellars and Best¹⁸ substantiate this lack of a nitrogen-saving effect with rats fed reasonable amounts of methionine in their basic ration.

So far no one has been able to supply any satisfying evidence that the catabolism of protein is actually caused by a requirement for any specific amino acid although after a burn one would anticipate a higher requirement of sulphur-containing amino acids to make good the loss of sulphur by

way of the skin than after a fleshy wound. As the writer⁶ has pointed out the partition of nitrogen and sulphur in the urine during the early days following injury is similar to that associated with the ingestion of protein in normal quantities.

Allison in his seminar discusses the nature of the protein which can be mobilized or catabolized during periods of protein or energy insufficiency. When these stores are reduced in malnutrition or disease, the body loses the capacity to repair damage, to build antibodies and to maintain the mechanisms which create barriers to destructive forces. This is a question of degree for it is only when depletion is carried beyond a certain extent that, for example, we find evidence of a failure to build antibodies. Recent work at the Rowett Research Institute indicates that the matter cannot be stated as simply as Allison makes out. Similarly, his statement that regeneration of destroyed tissues takes place only in the presence of sufficient nitrogen to create a positive nitrogen balance is an obvious overstatement.

Allison quite rightly points out that we have no evidence that there are any reserves of essential amino acids which can be drawn upon to supplement an inadequate diet without breaking down body proteins. He considers that the labile cytoplasmic proteins of the tissues—the protein stores—are different in character in the depleted state than in the normal which is presumably meant to mean that there is a quantitative rather than a qualitative difference. How far this is based on Roche's^{19,20} work is not clear, but her work so far has not been substantiated by further experimentation.

The reservoir of body protein is thus distributed in the tissues which with different capabilities supply nitrogen to the metabolic pool. The albumins are apparently more labile than certain globulins, and according to Allison different amino acid patterns favour the filling of one tissue compartment rather than another; one may be depleted while filling a second. Further, excess of one amino acid over requirements, e.g., me-

thionine, apparently reduces the retention of nitrogen. He reports that adding a large excess of methionine to casein in the diet will cause a loss of nitrogen from the skeletal tissues of the rat but will result in the building up of liver and kidney tissue. Feeding a protein source above an amount which produces maximum filling is obviously inefficient. It is perhaps a commonplace to state that all the constituents of the diet, including the minerals and water, play important roles in the maintenance, repair and growth of living tissues of which protein constitutes the bulk in all but the skeleton. When the caloric intake falls below 50 per cent of that which is adequate, the retention of nitrogen is markedly reduced.

In discussing the effects of the caloric level Allison refers to the work of Schwimmer et al.²¹ who have apparently demonstrated in man that retention of nitrogen was obtained at an intake of only 900 calories if the nitrogen and fat contents were sufficiently high. Williams et al.²² have reported that the retention of nitrogen in the rat was improved on a restricted diet if the fat content was high. These remarkable observations require confirmation and appear to run counter to earlier conceptions.

Allison also very rightly refers to the work of Benditt et al.²³ who found that the fabrication of a kg. of tissue in a growing rat and the reconstruction of a kg. of tissue in the adult protein-depleted rat demand the same quantities of structural material and similar constructing energies.

The contemporaneous changes in the serum proteins and lipids are also described by Peters. The early precipitate fall in albumin noted first by Cuthbertson and Tompsett²⁴ and confirmed by Peters²⁵ is coupled with a fall in lipid (Man et al.)²⁶ and obviously cannot be due to a general depletion of protein and lipid. Man has also shown that the serum amino acid nitrogen level also falls. These changes in albumin, lipid and amino acids happen only in patients who were previously in a healthy condition and are but further dislocations

of the metabolic processes which Peters considers are characteristic of impairment of the synthesis of protein. If this is so, it is not plain why Peters contends that "in chronic debilitating conditions since the synthetic powers of the body appear to be intact, administration of generous quantities of protein with adequate calories should be a major therapeutic objective, and delay should not await the termination of the catabolic phases." It is not sufficient to know that "there is no evidence that the administration of large amounts of protein during the catabolic phase is injurious." Further account should be taken of the experience of Hirschfeld et al.¹⁵ in burns when they found that the early administration of large amounts of protein to burned patients provoked nausea, vomiting, diarrhoea and other untoward symptoms. After the first few days their patients could tolerate larger intakes.

The pattern of events in protein depletion is not so clear cut as Allison outlines in his present contribution. For example, recent observations in Europe have shown that oedema may occur without a lowering of the plasma proteins much below the lower levels of what is regarded as normal. Allison points out that when an increase in α -globulin is found in the depleted animal this is due to a fall in the plasma volume rather than to an actual rise in α -globulin. A fall in plasma albumin and an increase in α -globulin appear to be associated with malnutrition, tuberculosis or cancer in man. When the α -globulin is reduced below normal in the protein-depleted dog, an increased susceptibility to infection results.

The cytoplasmic proteins of the liver are apparently the most rapidly mobilized of all proteins when animals are placed on a low nitrogen or protein-free diet. The production of haemoglobin, on the other hand, is sustained and when there is a real need for both haemoglobin and plasma protein, the protein flow in the animal depleted of blood and restricted in food protein favours haemoglobin formation.

THERAPEUTIC AND NUTRITIONAL
ADVANTAGES OF PROTEIN
HYDROLYSATES AND OTHER
AMINO ACID MIXTURES

Turning from the physiology and pathology of protein metabolism to the subject under discussion, namely, the evaluation of protein hydrolysates and other amino acid mixtures, we must note that the evidence available does indicate that nitrogen equilibrium can be maintained and the protein requirements of normal animals, including man, can apparently be met by means of an intravenous infusion of properly prepared hydrolysates of efficient proteins. This has now been carried through for twenty-four days without mishap.²⁷ But there is no evidence that intravenous injection of such preparations is superior from a nutritive standpoint to the normal method of eating, and all evidence favours the normal route when that is available. Much poor physiology and wishful thinking have actuated some workers in this field, and the difficulty of administration of hydrolysates has been glossed over by many workers. If hydrolysates are not injected very slowly, they provoke nausea and vomiting. According to Madden et al.,²⁸ mixtures of pure amino acids might have advantages in that they can be injected more rapidly and in higher concentration without untoward reactions.

One of the great difficulties of the intravenous route is the large volumes of fluid that have to be injected over a long period of time. Peters points out that it is seldom possible to give as a hydrolysate more than the equivalent of 75 Gm. of protein and 300 to 400 Gm. of glucose, a total of 1,500 to 1,900 calories per day. These prolonged operations are distressing to the patient and thus adversely affect recovery. Peters states that even if hydrolysates are given slowly enough to avoid nausea, patients cannot be induced to eat while they are being injected. Meals generally must be relegated to the evening and therefore interfere with rest.

If the patient is able to ingest, digest and absorb sufficient food, there is no need to

give some or all of it parenterally. When there is difficulty in ingestion, it may be necessary to provide highly nutritious fluid drinks, with skim milk as the main protein constituent. It has been recommended that when necessary advantage should be taken of the sense of thirst in order to secure adequate nutrition.

Peters finds no justification for the use of hydrolysates by mouth whether by ingestion or by tube, and he contests Co Tui's²⁹ contention that such preparations are more easily utilized than undigested proteins as being unsupported by physiologic evidence. With this the present writer is in entire agreement. The evidence of those who attempted to supply protein hydrolysates to gravely starved people in Holland and in Belsen Concentration Camp has shown that intact protein can be tolerated and utilized by these people. When intravenous therapy was necessary, plasma was the safest treatment.⁴²

The observations of Riegel et al.³⁰ indicate that the excretion of faecal nitrogen is greater when hydrolysates are given than when whole proteins are given. Hydrolysates or amino acid mixtures fed intravenously cause an increased urinary excretion of amino acids and peptides, but usually this does not materially affect their nutritional value. On the whole, oral feeding of hydrolysates or amino acid mixtures is more efficient than intravenous feeding. The loss of amino acids and polypeptides through excretion in the urine is greater the higher the rate of infusion.

Peters draws attention to one useful application of intravenous hydrolysates, namely, when it is absolutely necessary to secure complete rest of the alimentary canal. In conditions such as acute mercury poisoning the evidence indicates that not even water should be taken by mouth. If complete rest can be achieved, this should end the characteristic vomiting and diarrhoea.

Homburger in his review very rightly stresses the difficulty in evaluating the nutritional status of a patient in respect to protein—one of the most complex of all

subjects. Some now consider that "the state of health" is a more embracing term, but the means of assessment are not thereby simplified. Homburger draws attention to the misleading interpretation which may arise from an assessment of protein depletion by analysis of the total plasma, albumin and globulin. As was pointed out earlier recent evidence has shown that protein depletion may exist without any marked depletion of these proteins.

It is pertinent to what has already been stated that Homburger in his review of the various types of hypoproteinemia gives little if any indication for the infusion or oral administration of protein hydrolysates. When protein has to be infused, it is recommended that plasma be given unless there is a complicating anaemia for which a blood transfusion would be the best line of treatment.

Allison points out that acid hydrolysis of protein destroys tryptophan and, to a much lesser extent, sometimes methionine and that there is also a destruction of certain essential polypeptides. Alkaline hydrolysis leads to marked racemization and cannot be recommended. The work of Chow, Allison and White³¹ has shown that the utilization of casein by the dog and rat is not altered by enzymic hydrolysis, the hydrolysate having the same growth value in dogs and rats as the unhydrolyzed casein. A 60 per cent enzymic hydrolysis does not alter the streptogenin content which is essential for proper utilization.

One of the difficulties encountered by the reader of a series of seminars on a debatable topic dealing with treatment, such as the one under discussion, is to discern the wise procedure when experts differ. Young in his contribution to this symposium clearly indicates that the intravenous route should be chosen only when other methods of feeding are impossible. He adds that the best protein hydrolysates still do not permit convenient administration of the large amounts of nitrogen indicated in many postsurgical cases. Young then proceeds to comment on

chemical considerations in the selection of protein hydrolysates.

The proteins which are mostly used for the production of hydrolysates are casein, lactalbumin, muscle, blood, liver and yeast protein but sometimes a mixture is used. The resulting product must of course be non-antigenic and have a low concentration of dicarboxylic amino acids as these are held to be nausea-provoking. Stability in solution and availability for infusion at a rapid rate are also necessary attributes. Furthermore, there must be an adequate energy intake to permit optimal use being made of the hydrolysate. In the writer's view it is doubtful if much attention need be paid to the vitamin side if the emergency requiring this intravenous feeding only lasts a few days.

This writer does not agree with Young's summary of the advantages to be gained by hydrolyzing proteins for oral use for so far no real evidence has been adduced that the hydrolysates by mouth are to be preferred to intact protein in cases of impaired digestion. As has been discussed earlier some doubt exists as to the real basis of the enthusiastic reports of Co Tui on the use of oral hydrolysates. Although they are as a rule completely soluble, the unpleasant taste or nausea-provoking attributes of oral hydrolysates are such as to undo the possible benefits to be derived from their complete solubility. Young later stresses the disadvantages of hydrolysates but it would have been better had he weighed these against the possible advantages and given a considered judgment. There is no doubt but that all protein hydrolysates marketed should have the information which Young advises clearly marked on their labels.

Werner in his seminar dealing with the problems of parenteral nutrition wisely points out that it is still debatable whether the results of routine parenteral feeding warrant the risks and discomfort to the patient as well as the expense. Werner's own work has shown that protein hydrolysates given in the postoperative period to patients undergoing subtotal gastrectomy for peptic

ulcer provide no definite evidence of a gain over a control series of patients treated exactly the same way but without the parenteral nitrogen. Werner draws attention to the effect on nitrogen balance of accidental or unavoidable interruption of parenteral feeding and points out that the extent of the caloric intake which must be provided with protein has not been entirely settled.

After prolonged periods of undernutrition the existing depletion of nitrogen stores may lead to hypoproteinaemia due to inability to meet the increased demands for nitrogen associated with operation. All the indications are that repletion is more readily accomplished before operation, that is, before the postoperative catabolic period ensues. The indications for parenteral feeding are inability to ingest, digest or absorb adequate quantities of food over a period of time which jeopardizes the chance of an uneventful convalescence or may even prejudice survival.

Werner considers that the rationale for employing the parenteral route before operation when oral or tubal feeding of intact protein is not available rests more on the necessity to restore liver function and to facilitate adaptation to a more vigorous nitrogen turnover than on the need for building up a store of nitrogen. It is admitted that the amounts of nitrogen retained during such treatment are quite limited due to the inadequate provision of calories. But this type of therapy is probably justified, especially in conjunction with plasma or whole blood.

In his discussion of proteins available for infusion Werner points out that when human plasma, whole blood or serum albumin are given intravenously to restore the blood volume and osmotic relationships they are also available for nutrition. If it is hard or impossible to sustain an adequate energy intake, the attempt to restore the circulating proteins and tissue proteins should be made as short as possible, otherwise, the patient's condition may deteriorate still further.

The present writer is not at all certain of the soundness of Werner's argument when he advises that once the parenteral administration of high nitrogen levels has begun, either before or just after operation, they should be continued for the first few days after the operation or otherwise the sudden discontinuance or reduction of the nitrogen intake for one or two days will result in sharp losses due to the fact that the nitrogen excretion continues at the same level as if the high intake had continued. While that may be so, the evidence indicates that the organism is geared in a catabolic or anti-anabolic phase immediately following injury. Further, the evidence does not fit Werner's statement that reduction in calory and protein intake after injury, plus the added demands of both during the febrile period, probably explains in large part the protein catabolic period. I would agree with Werner in his view that the use of hydrolysate and amino acids by vein should at first be limited to those postoperative patients in whom previous protein depletion has occurred and cannot otherwise be replenished preoperatively, and secondly to those in whom evidence of a postoperative complication has already appeared.

The rate of disappearance of plasma proteins from the blood stream to the tissues diminishes as the tissue stores are replenished. Werner finds that nitrogen balance studies reveal a great difference in the ease with which nitrogen given as preformed plasma or as red cell protein provides a positive balance as compared with nitrogen given as split protein in the form of hydrolysate or amino acids,³² the difference being due to the increased excretion of nitrogen with the latter. This difference is apparently comparable to that seen when serum protein or whole blood is given by mouth.

While the lag in excretion of intact protein by vein results in greater efficiency of utilization than can be obtained by amino acid mixtures, Werner considers that there is evidence that the provision of a flow of amino acids to the liver is essential for

the maintenance of normal liver function. The lipotropic action of these substances, especially methionine, is apparently not obtained when preformed serum protein is injected.³⁴ The fatty liver of starvation is prevented or alleviated by food protein by mouth or by parenteral hydrolysates but not by intravenous blood or plasma and, according to Varco,³⁵ blood or plasma by vein fail to prevent death of semistarved patients following extensive and prolonged surgical operation. Nevertheless Varco has presented evidence in support of his view that the ingestion of protein as a preoperative preparation is as effective as, or more effective than, corresponding increments made available to the patient in the post-traumatic interval. The writer believes that there is some merit in Kremen's³² suggestion that a mixture of plasma and hydrolysate or amino acids might be useful.

It should be noted that cardiac or renal dysfunction or both together may prevent toleration of intravenous feeding. Reactions to parenteral hydrolysates are few if pyrogens are removed, and the infusion tubing is renewed or treated with sodium hydroxide. As already mentioned nausea and vomiting may result from too rapid an infusion rate and Werner advises rest periods after infusion and the introduction of not more than 50 Gm. amino acid mixture at any one time.

Elman prefaces his article, the final one of the series, with a plea for clarity and uniformity in nomenclature when describing preparations for clinical use. He prefers that the term 'amino acid mixture' be used to include both the pure crystalline material on the one hand as well as protein hydrolysates (or digests) on the other. This term would thus also include mixtures of amino acids and peptides. One reason for using the term amino acid mixture in place of protein hydrolysate is that it would exclude gelatin which is not really a hydrolysate but is slightly hydrolyzed owing to the method of its extraction. Elman would retain the term hydrolysate to preparations in which the digestion has been carried

out for purposes other than the production of amino acids or small peptides for nitrogenous nourishment. It is doubtful if Elman's suggestion will bear much fruit.

Elman provides an excellent historical summary of the development of these various amino acid mixtures produced by compounding mixtures of amino acids in both the natural and racemic forms and of enzymic and acid digests. In some preparations larger fragments have been removed and in one, aspartic and glutamic acids are removed and the product lyophilized. It is pointed out that as these amino acid mixtures act as a buffer, the pH of the mixture should be adjusted so as to have no really significant action on the acid-base balance.

That nausea and vomiting may also be caused by unnatural amino acids has been shown by Howe et al.³⁶ in dogs; particularly was this the case with *D,L*-methionine. Glycine improved the tolerance. It appears that mixtures of the essential amino acids and glycine can be tolerated at faster rates of infusion than with actual hydrolysates. But certain peptides or larger fragments may be necessary or beneficial to man in the long run. Elman points out that the evidence indicates no difference in nitrogen balance between a partial protein hydrolysate containing 75 to 83 per cent of its nitrogen still as peptides when injected and a complete hydrolysate injected at the same minimal level, and this even in spite of the large excretion of peptides and amino acids with the partial hydrolysate. Elman considers that this indicates that something was present in the retained part of the partial hydrolysate which improved nitrogen balance. The work of Christensen et al.³⁷ suggests that the peptides of a casein hydrolysate (amigen) appear to be less readily utilized by the tissues and more poorly retained by the kidneys than pure amino acids. Both sets of observations require confirmation. There is some unconfirmed evidence that the peptides from a partial acid hydrolysate are more efficiently utilized than those from an enzymic hydrolysate.

Elman rightly points out that since all the amino acids that go to form body proteins are essential to the body it is preferable for an amino acid mixture (or digest) to have both dietary essential and unessential amino acids present for maximum efficiency.

According to the work of Kade et al.³⁸ and Silber et al.,³⁹ the intravenous route in the dog is as satisfactory as the oral route as far as nitrogen balance is concerned, whether the test is with crystalline amino acids or with a hydrolysate. But in man it has been found that a lyophilized acid hydrolysate of casein gave better nitrogen balance when given by mouth than when injected. This is what one would expect from animal experimentation. It would appear wise when dealing with acid hydrolysates to fit the hydrolytic method to the protein concerned. According to Kozoll and Mok,⁴⁰ a 1,000 calory intake was optimal for nitrogen balance, and intravenous feeding beyond this did not improve utilization.

Casein hydrolysates are sometimes used at 5 to 10 per cent concentration and mixtures of pure amino acids at 8 per cent. In ten healthy males Werner was able to substitute 60 of the 90 Gm. of protein in the diet with an intravenous amino acid mixture with no change in the nitrogen balance. The subcutaneous route seems to be feasible for both pure amino acid mixtures and hydrolyzed protein. Indeed Madden et al.⁴¹ thought that this route in the dog was better than the intravenous route. The intraperitoneal route is definitely unsatisfactory.

Elman routinely uses 100 Gm. each of amino acid mixture and 100 Gm. glucose in 2,000 cc. solution containing about 5 Gm. sodium chloride. This he gives in two 1 L. injections as 5 per cent hydrolysate and 5 per cent glucose, one in the morning and one in the afternoon or evening. Each injection usually takes two hours. This seems a reasonably safe procedure. Parenteral vitamins are injected as required. Attention is drawn to the tendency toward venous thrombosis and glycosuria which may result if 10 per cent glucose is used for infusion. Glucose, 5 per cent, in normal

saline is well tolerated, however, but this means that considerable volumes are required to make up the energy intake required in the twenty-four hours. Use of fat emulsions for intravenous work is still in the trial stage and there are grave difficulties and dangers.

Werner and Elman both draw attention to the necessity of taking account of the electrolyte content and its relationship to the source of the protein hydrolyzed. Thus, hydrolysates from animal cells contain much potassium and magnesium; fibrin and casein hydrolysates contain relatively little salt and that mainly sodium.

When the use of hydrolysates is indicated, it is necessary to ensure that the protein used is a complete source of all the essential amino acids. The presence of polypeptides tends to limit the tolerance and speed of administration. It is not quite certain how necessary these larger fragments are to man as most experiments with pure amino acids have been of relatively short duration. When hydrolysis is practically complete and any deficiencies have been made good, it is apparently possible to infuse at a rate comparable to that at which glucose itself can be given. If only the laevorotatory forms are given, economy in material is considerable as the unnatural forms are usually inactive physiologically unless they are converted into the natural isomerides.

Elman agrees that the calory requirements are but inadequately met by such a parenteral diet. But is it wise to leave the rest of the energy needs to be met by adipose tissue? Elman considers that further evidence has confirmed that this is safe and he advises that for short periods of time at least the glucose intake can be safely limited to 100 Gm. Ketosis does not arise. Such a low calory intake obviously will not lead to the deposition of much tissue protein, but it will minimize the metabolic loss of protein. Elman freely admits that full tissue repletion can probably be achieved only through normal oral feeding. The need for parenteral amino acid mixtures is

frequently coupled with a need for blood or plasma.

There does not appear to be any real evidence that hepatic disease is a contraindication to the injection of amino acids. Elman would extend the use of amino acid mixtures, including hydrolysates, but the present author does not concur in this unless other means of nutrition are denied the patient.

Elman concludes by pointing out that protein hydrolysates and pure amino acid mixtures are utilized by the body and can be given safely by vein in all conditions in which one would in the past have had to inject glucose as a necessary source of nourishment. Suitable patients include those who are unable to ingest, digest or absorb sufficient food over a period of time or who must secure complete gastrointestinal rest. It is stressed that there must be clear proof that such rest is absolutely necessary.

SUMMARY

Available evidence indicates that nitrogen equilibrium can be maintained and the protein requirements of normal animals, including man, apparently met by intravenous infusion of properly prepared hydrolysates of biologically efficient proteins. But there is no evidence that the intravenous route is superior from the nutritive standpoint to the normal method of feeding. Indeed, if hydrolysates are injected too quickly, nausea and perhaps vomiting may lead to less efficient use of the amino acids and peptides. It is seldom possible to give routinely more than the equivalent of 75 Gm. protein and 300 to 400 Gm. glucose by the intravenous route. There does not appear to be any solid evidence for the use of hydrolysates orally or by tube into the alimentary canal.

While there is abundant evidence of the life-saving benefits which immediately accrue from the use of whole blood or plasma, these proteins also serve as a source of nutrition. There is some doubt whether the intravenous use of intact proteins will permit certain effects which are bound up with

intermediary metabolic changes which follow the ingestion of protein in the food or the infusion of amino acid mixtures by vein. Mixtures of pure amino acids lack certain peptide fragments which may be necessary for growth and the full maintenance of nutrition. To save body protein it may be wise to include all the amino acids rather than to rely on the essential amino acids plus glycine.

The rationale for employing amino acid mixtures parenterally in place of, or along with, intact blood proteins rests more on the necessity to sustain liver function and to maintain a more vigorous nitrogen turnover than to the need for building up a store of nitrogen. This line of treatment may be worthy of further exploration.

Because of the difficulty of infusing sufficient protein and energy in the infusion fluid, it is generally agreed that it is not possible to make good the requirements of the protein-depleted organism entirely by intravenous injection. It is not wise to give fluid containing more than 5 per cent hydrolysate and 5 per cent glucose. Mixtures of pure amino acids may be given at 8 per cent strength. Even these levels necessitate some four hours to provide 2,000 ml. The whole procedure causes discomfort if not actually distress to the patient and also prevents rest. The calory requirements are but inadequately met by these procedures although it is held that for short periods of time the glucose intake can be safely limited to 100 Gm., the rest of the energy needs being met from the adipose tissue and the 100 Gm. of hydrolysate preventing further protein loss. More corroborative evidence is required on this fundamental issue.

It may be wise to restrict the use of intravenous hydrolysates and mixtures of pure amino acids to postoperative patients with previous protein depletion which has to be corrected preoperatively and sustained postoperatively, and secondly to those in whom evidence of a postoperative complication has already appeared.

Amino acid mixtures including hydrolysates are of value in treating conditions in which it is absolutely necessary to have complete rest of the alimentary canal, for example, in acute mercury poisoning.

Indications for parenteral feeding are inability to ingest, digest or absorb adequate quantities of food over such a period of time as to jeopardize the chance of an uneventful convalescence and which may even prejudice the chance of survival.

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Clinic on Psychosomatic Problems

Feeble-mindedness or Pseudoretardation?

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Pediatric-Psychiatric unit of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr. Foundation.

DR. SAMUEL KAPLAN: David J. (Unit No. 593549), a seven and one-half year old boy, was referred to the Pediatric-Psychiatric Service by a psychologist who had examined him and found evidence of mental retardation but was puzzled as to the cause of the intellectual deficit.

When the mother brought the patient to us, she asked primarily for advice on how to manage him and for an evaluation of his smallness of size. She described him as a very small, very "queer" boy who had developed slowly. She said that David always tried to compete with his bright twelve-year old brother and inevitably failed. He had been rather anxious during the previous summer which the mother attributed to his fears of failing in school. The mother also reported inconsistencies in his behavior. For example, he insisted upon having his parents dress him and at times feed him while in other ways he was precocious. He rowed a boat alone at five and helped to deliver newspapers at seven. At the time of referral David was attending a slow class in a public school where he was popular with his playmates.

Details of the family background were given by the mother, a thirty-eight year old professional woman, who was obviously tense and displayed a lack of appropriate emotion when discussing her husband's family and her son's difficulties. Her husband, she said, was a "tower of strength." He was a thirty-nine year old attorney who had never practiced law and who was employed as a sales manager. During the war years he had worked as a civilian employee of the Army and had been away from home

for extended periods. The family had moved many times during those years.

There was a history of severe mental disturbances in the father's family. The father's mother, grandfather and two other relatives committed suicide and a younger brother became psychotic. In the mother's family a younger sister was said to have hysteria and the patient's maternal grandmother was described as a "cold" person. David's only sibling was the twelve year old brother who was apparently normal.

Past history revealed that the patient was born prematurely with a birth weight of less than 3 pounds. He had been in a precarious condition with cyanotic episodes and the mother was told that he probably would not live. At the age of three months he was again in a critical condition with bronchitis. After this he got along well and the motor aspects of his development seemed only slightly retarded. He sat alone, crawled at eight months and walked at eighteen months. However, he was markedly slow in his speech development and did not talk until he was four years of age.

The mother described the boy's background to our social worker and during this series of interviews a number of significant factors appeared. Although apparently anxious to help him, she nevertheless discussed him in a detached manner, referring to him as a "fascinating case study." The mother was superficially tolerant and affectionate and yet could not permit him to express any aggression. Her own hostility toward David was evident from various incidents which she discussed. As an example, she had once found it very difficult to tell him not to play

on a certain broken footbridge. She knew that if she had allowed it he would undoubtedly have been drowned.

The mother said her husband was overindulgent, overprotective and very affectionate toward David. However, he had been a shadowy figure during the first six years of David's life by reason of his long absences. The father currently was working until nine or ten every night and saw the boy only during week-ends. The mother had recognized David's concern over the absence of his father and reported that during the previous summer, when the family lived together as a unit for the first time, he had seemed puzzled as to the place of the father in a family.

The patient's brother was openly hostile and rejected him constantly. When David was three years old, the brother had been sick for almost a whole year and had required so much attention that David was more or less forgotten. There was a repetition of this sequence when David was five. The mother emphasized the marked jealousy that David expressed toward his brother. The past summer the mother had had to leave suddenly because of her father's illness and David had been "deserted" again.

Physical examination in the Children's Medical Clinic revealed nothing abnormal. The patient was small for his age but not unusually so and there was no evidence of any endocrine dysfunction. A neurologic consultant was unable to find any clinical signs of old brain injury. However, the electroencephalogram was definitely abnormal and Dr. Abbott will describe it for us.

DR. JOHN A. ABBOTT: This electroencephalogram is an abnormal record. It shows notably: (1) slow activity, diffuse, symmetrical and more marked posteriorly and (2) a paroxysmal breakdown in the first minute of overbreathing. In more detail, with normal breathing there is probably low voltage beta activity anteriorly; irregular and some regular at around 10 per second posteriorly; waves at about 2 per

second and 100 microvolts posteriorly and other slow waves diffusely. With overbreathing there is breakdown in the first minute with bilaterally synchronous 3 per second paroxysmal activity to 125 microvolts anteriorly and ragged activity posteriorly.

DR. KAPLAN: The psychological tests were very helpful and perhaps should be discussed at this point in the presentation.

DR. ELIZABETH M. HINCKS: I first gave him a performance test, the Merrill-Palmer test. He had a mental age of five years three months and an I.Q. of 68. He showed up poorly in form and space relations. He seemed to enjoy the test and was cooperative. The next time I gave him a Stanford-Binet test. Then he had a mental age of five years nine months and an I.Q. of 75. He did not enjoy this test so much. At times when it seemed he did not know the answer, he talked in a silly fashion and almost "free-associated." When we got to the part about repeating numbers he said: "No more numbers" over and over. His language development was better than his ability in mechanical and spatial relations. He passed all verbal tests at five years, pictures at six years, sentence memory at seven years and similarities at age eight. He seems to have special defects for form and space, rather than memory and reasoning difficulty.

DR. SAMUEL WALDFOGEL: The patient was given the Rorschach test and the following interpretation was made: Supporting the possibility of mental defect were the stereotypy, lack of any movement, apparent lack of shading and the appearance of several very poorly structured forms. However, in contradiction we found extremely rapid syntheses of the blot (usually the whole) several of which were quite adequate and the absence of oligophrenic details. It seemed quite possible that this boy's intellectual defect resulted primarily from an attentional deficiency. One might postulate that because of his extreme impulsivity he could make only brief and superficial contacts with his environment which on the one hand constantly attracted him and

on the other hand seemed to frighten him. Apparently he was neither able to control his own emotions nor make adequate relations to others. The complete loss of control on the polychromatic card indicated the extent to which affect was a disruptive influence in this boy and added evidence that his intellectual deficiency stemmed from his turbulent emotional life. The severity of this boy's personality problems, whether or not he was mentally retarded, could not be minimized and the possibility of some diffuse cerebral lesions had to be taken into account.

DR. KAPLAN: On the basis of the history of prematurity, neonatal cyanotic spells, slight retardation in the development of motor skills, marked retardation in acquisition of speech and the abnormal electroencephalogram, it was believed that the patient probably did sustain diffuse brain damage (either from hemorrhage or anoxia) at the time of birth. However, because of the obviously disturbing family relationships and the clues given by the psychologic tests we decided to study the psychogenic factors by means of weekly interviews in the Out-Patient Department.

At first David showed evidence of great tension. He was a small, wiry boy with a worried, old-looking face. He talked constantly and rapidly, running many words together, omitting syllables and using many infantile expressions. In contrast, however, he used many polysyllabic words quite correctly. Physically he was restless and overactive and the therapist sensed great anxiety in his speech and activity. During the early interviews David was much preoccupied with the subject of magic, emphasizing over and over his belief that one could accomplish things only by making use of magic. (His brother was an amateur magician and could make objects disappear.) He was very boastful, seeking praise constantly and at the same time being unable to tolerate the slightest criticism.

After about two months David's behavior changed. He became less active and there was slight improvement in his speech. It was then that he introduced two themes into

the interviews. One of these, elaborated upon in great detail during subsequent visits, was his desire to eliminate his father from the home. The other was a wish to kill his mother, and this was dropped for a long time, only recently being expressed again.

The interviews very clearly illustrated David's wish to kill his father, his fear that the father would annihilate him in retaliation and his consequent overwhelming feeling of anxiety and insecurity. In one session David greeted the therapist by pointing a toy pistol at him and shouting: "Stick 'em up!" He "forced" the therapist at gun point into the office and then spent the next half hour "killing" him by a variety of means. His fertile imagination in this and other interviews was quite in contrast to the picture presented by a dull child. He pretended to throw the psychiatrist from a ship; he turned on a radiator saying that it was a jet of poison gas and devised other ways of punishing him. At the next interview he burst into the room shouting: "I'm the police. Who killed David's father? Did you? You did! I'm going to shoot you," and proceeded to do so. The therapist denied the accusation and reminded David that he himself had done so in play last week. This resulted in mounting anxiety and the opportunity was taken to explain that neither one had *really* killed David's father. The therapist went on to say that lots of little boys wished they could get rid of their fathers, and then they got terribly frightened because of their feeling that their father would punish them for this wish by killing them. David listened very attentively and then asked: "What would the father do? Would he kill the boy?" He was reassured that the father would understand and, since a wish is not a deed, the boy would not be punished at all. This sort of explanation was repeated several times and there was no more shouting and killing by David.

In subsequent interviews David again expressed ideas that his father might kill him and the only solution was to get rid of the father first. However, in his play he no longer acted out the killing himself, but

pretended to be the informer who called the police; he was then a gleeful onlooker as the police arrested and killed his father. More recently the object of his aggression has been the therapist rather than the father.

After about five months he returned to the theme hinted at in earlier sessions, namely, his wish to kill his mother and the fear that she would take revenge upon him. The latter element came out clearly during his play one day. He was acting out the rôle of the mother and went to the doll house and shot the baby doll with a toy cannon. (In previous sessions he had clearly identified himself with the baby doll and had given it the name of David.) In a subsequent interview the patient made the mother doll go up to the roof of the doll house to punish the baby for being there. He then "accidentally" pushed the mother off the roof and soon repeated the act. When the therapist remarked that the mother seemed to be falling, David picked up the doll again and said: "I'm going to throw her out of the window." He then repeated a former sequence: He cast the therapist in the rôle of David and he became the policeman who arrested David and executed him for killing the mother. Again he was reassured repeatedly that the mother was not really dead, that it was only his *wish* that she be killed, again emphasizing that the wish is not the equivalent of the act and is not punishable. He refused to accept this reassurance, and at the present time this problem is the central one in the therapy.

During the period of therapy (about six months) there have been definite changes in David. His speech has improved markedly and he has lost the air of tension and anxiety. He is more self-assertive and no longer needs help in dressing, eating, etc. He is doing well in school, is at the head of the slow class and is to be promoted. His attention span has improved to the point where he can now complete all of his school papers, something he could not do last term.

DISCUSSION

DR. NICHOLAS D. RIZZO: His general behavior during the picture projection test

was extremely impulsive. His associations were very hard to follow and at times his responses were not at all pertinent to the card shown. When we came to the picture of the male nude, he saw it through a window although there is no window in the picture. He spoke of many things but denied seeing the nude. When I showed the picture of the female nude, he almost snatched it from my hand. On the whole he dealt with the picture situation poorly and in the first part of the test he killed his mother in three of the pictures.

DR. GEORGE CARTER: In regard to the tests, does not his doing well verbally rule out mental retardation?

DR. HINCKS: I do not think we can call his mental age figure a flat fact at this time. When I saw him, without having heard all this, I thought there might be brain damage or something permanently wrong. This picture is not that of feeble-mindedness. He seems retarded but not defective. His reasoning, vocabulary and memory are all very good. His rapidity of motion, the activity of his aggressive fantasies, the variety of things he thinks to do are all not in accordance with feeble-mindedness. I would not make a diagnosis of intellectual deficit yet.

DR. CARTER: Do mentally defective children have so much anxiety?

DR. HINCKS: The borderline patients who have to compete with children of higher I.Q.'s get hysterical blindness sometimes. They get anxiety because they have to compete.

DR. ALLAN M. BUTLER: They get hysterical temper tantrums when frustrated by their own incompetence.

DR. GERTRUD REYERSBACH: Some appear to be retarded when they are slow in speech development but you cannot call them defective. Later they are able to talk very well.

DR. HINCKS: This boy felt rejected. He might not have had any incentive to talk before.

DR. BUTLER: This is a fundamental problem in the value of the I.Q. If a boy has an I.Q. of 70 and yet you see the boy is not retarded but is emotionally blocked,

it limits the value of the I.Q. as a diagnostic factor. Certainly the psychologists ought to be refining the tests to make this important distinction.

DR. HINCKS: It is not the tests that need refining. You need an examiner and interpreter of the tests who has a great deal of experience and knowledge of these different types of children. An I.Q. may be an incorrect index of the mental capacity of the child.

DR. CARTER: Do you think a test invalid when you find scatter?

DR. HINCKS: Scatter might indicate brain damage, too. You have to take all the variables into consideration.

DR. STANLEY COBB: This is a very important case because it brings up the diagnostic differentiation: *amentia* vs. *dementia*. If the former, it is "lack of mind," a permanent and hopeless defect. If "dementia," it is more or less loss of a mind once present and the prognosis can be good. The tests for I.Q. given by Dr. Hincks showed a low score but were not typical of mental defect (*amentia*). Dr. Waldfoegel's Rorschach test and Dr. Rizzo's picture test gave evidence that the child was emotionally disturbed and not "mentally defective" in the primary and hopeless sense in which that term is usually used. The history as learned by psychiatrist and social worker gives plenty of evidence that the boy was in a family situation which caused him to feel deeply rejected. Dr. Kaplan's patient therapy over six months not only improved the boy's emotional reactions and intellectual ability but also brought out more evidence that he felt rejected and was full of anxiety, fear, hate and guilt. In other words, his emotions were blocking his use of his perfectly serviceable mind. Thus we have a right to say that he has no "*amentia*" but a beginning and not too serious loss of ability to use his mind (*dementia*). There is no neurologic evidence that his brain is injured, but we cannot pass over the history of premature birth and cyanotic spells and the abnormality of the electroencephalogram without admitting that there may have been cerebral damage. Nevertheless, dam-

age to the brain does not always, nor even often, cause intellectual defect. The brain has a great reserve and a brain injured in childhood may remain a perfectly serviceable organ for intellectual development. The child may not go as far as he might have with a perfectly normal brain; he may be more unstable; he may even become epileptic later. But the functional capacity of the brain remains within what we call normal limits, arbitrarily scored as I.Q. between 90 and 130.

That is what I think about this boy. He has a good enough brain to get along in the world if we only can relieve him of his emotional stress which is now blocking progress. Dr. Kaplan is making good progress.

The prognosis depends upon therapy. If our good team-work of psychiatrist, social worker and psychologist with patient and mother continues, I feel hopeful of a good result. If the treatment of child and mother is interrupted, the outcome may be disastrous. Children with as great a load of rejection and fear as this boy has may go into a regressive type of behavior that is said to become permanent. At least many sufferers from it seem to have become set in their ways and spent their lives in institutions for the mentally ill or defective. Heller* described extreme cases of this sort in 1908 under the name of *Dementia infantilis*. He speculated as to the various possible causes, but did not express his own opinion as to whether such cases were due to emotional stress, cerebral lesion or hereditary schizophrenia. Not much progress was made in the next thirty-five years, but recently Bender in New York, Putnam and Rank in Boston and Yakovlev in Connecticut have discussed these cases. It is obvious that somewhat similar clinical pictures can occur from each of the three causes mentioned. The present need is for better diagnostic methods and more clinical acumen. Then the patients with good prognosis can be

* HELLER, T. Über Dementia infantilis (Verblödungs-progress im Kindesalter). *Ztschr. f. d. Erforsch. u. Behandl. d. jugendl. Schwachsinns*, 2: 17, 1908.

chosen for therapy and those who are hopeless patients sent to custodial institutions.

DR. LUCIE JESSNER: Observation and treatment of this boy, who has a family background of serious mental disturbance and signs of brain damage shows the interrelation of various factors producing a psychiatric disturbance. Fifty years ago one would have probably made a diagnosis of retardation on the basis of brain damage and would have considered psychotherapy futile. Psychologic tests showed good reasoning powers in spite of disturbances in special fields and revealed the strong factor of anxiety in his performance. Psychiatric study showed the influence his life experience had in creating uncertainty and confusion—a child rejected by his mother who consciously wished to kill him and lacking the presence of his father in most of his earlier years. In psychiatric interviews his fear of being killed and robbed of his penis are expressed. It is not surprising that in this atmosphere of hostility he is unable to restrain his own aggression. Being aware of his own dangerous impulses, his anxiety increases because he expects punishment for his intentions. In psychotherapy he was allowed to express his feelings in words and in play and was informed and reassured about the difference between doing something “bad” in fantasy and the actual carrying out of such a threat. He has shown a remarkable improvement in his speech and I believe that this is due to the fact that he learned with Dr. Kaplan that he can tell in clear words what he thinks without being punished for it. His behavior on the whole seems less fearful and erratic. It seems most desirable to continue treatment, as this boy in spite of his central nervous system disturbance is capable of developing. It also seems important to continue working with the mother toward the goal of accepting this child.

SUMMARY

This case was presented to illustrate a not uncommon problem in the field of child psychiatry. A boy who is a “retarded” child

was referred for evaluation of his apparent intellectual deficit. The history and the abnormal electroencephalogram furnished some evidence that he had suffered neonatal brain damage. This in itself could account for the clinical picture but on more careful scrutiny of the family relationship, certain factors were noted: the patient's rejection by his mother, the years of early life when his father was literally a missing figure in the family, and the long periods of neglect due to the brother's sickness.

The Rorschach test was of help in clarifying the problem as it indicated much anxiety and a severe personality problem in addition to the possibility of diffuse brain damage. It was brought out in the discussion and is worth re-emphasizing that the I.Q. is not always a correct index of the mental capacity of a child. The retardation may be due to severe emotional disturbances rather than feeble-mindedness.

Psychiatric interviews confirmed the suspicion that the patient was a very insecure, anxious and emotionally disturbed child. During six months of therapy he showed a capacity for change and development. It was therefore believed that the mental retardation was not due primarily to innate lack of capacity but was largely a “pseudo-retardation” caused by an emotional disorder. Two conditions apparently existed: (1) cerebral damage dating back to birth and (2) superimposed neurotic disturbance. One might regard the brain damage as one of life's handicaps with which the patient must contend. His progress in psychotherapy has been encouraging thus far and further improvement is anticipated.

The technics used in psychotherapy with children will not be described here as good discussions are available.* The interview material, however, was cited in some detail to bring out certain points. Once a good relationship has been established with the child, one can learn a great deal from observing his play. The “acting-out” of

* WITMER, H. L. *Psychiatric Interviews with Children*. New York, 1946. The Commonwealth Fund.

fantasies by means of dolls or by assigning roles to patient and therapist is extremely helpful. This boy expressed very clearly the common childhood belief in magic and in the "omnipotence of the wish." One can thus understand the tremendous anxiety with which he was burdened. It is important

to note that reassurance is not given indiscriminately, but is given along with an explanation that the child's specific fears are not really true. In this case, the wishes that the parents should die were acted out very clearly and thus explanation and reassurance could be given with confidence.

Clinico-pathologic Conference

Diabetes, Fever of Unknown Origin and Coma^{*}

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, C. S., (B. H. No. 143684), was a fifty-six year old, white married housewife who entered the Barnes Hospital on February 4, 1947, complaining of chills and fever. The family history was irrelevant but the past history was of interest in that the patient had been known to have diabetes for eight to ten years; for some of this period she had apparently followed a diabetic diet but had never taken insulin. Her general health had evidently been good until three years before admission when she had a febrile illness characterized by a temperature ranging from 101 to 104°F., associated with chills. The episode lasted approximately six weeks but no diagnosis was established. The patient resided in a small town in Illinois and frequently visited relatives in the nearby countryside where she drank well water and milk which was probably unpasteurized. During the winter prior to her admission to this hospital she had cleaned pheasants upon several occasions, the last time two weeks before entry.

Ten days prior to admission the patient developed malaise and her temperature was found to be 101°F. On the following day she developed pain in the flank which persisted. Her temperature elevation likewise continued at approximately 101°F. She refused medical attention for three days but then consented to enter the local hospital. During her hospitalization there she was given 40,000 units of penicillin

every four hours but despite this therapy her temperature ranged between 101 and 103°F., and she had one or more chills daily. Three days before entry the patient became comatose, presumably because of the onset of diabetic acidosis. Information regarding laboratory studies at the outside hospital were as follows: On admission the urine sugar was said to have been 3+ but no acetone was present. The blood sugar was 250 mg. per cent. On the third hospital day the urine sugar was 4+ and the urine was positive for acetone. On the same day the white count was 7,800 but it subsequently fell to 3,600. Smears for malarial parasites were negative. The patient was given insulin therapy and glycosuria and acetoneuria were said to have been controlled. Because her temperature continued to spike, she was seen by a consultant who advised immediate transfer of the patient to the Barnes Hospital.

At the time of entry the patient's temperature was 40.3°C., pulse 100, respirations 26 and blood pressure 164/80. The patient was stuporous and appeared acutely ill. Her face was flushed and the skin was generally hot and dry. Respirations were not labored but the patient groaned with each expiration. There were numerous ecchymoses, presumably the sites where insulin was injected. Although one or two suggestive petechial spots were noted, no generalized eruption was present. The pupils were small but reacted normally to

^{*} From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

light and accommodation. The eyegrounds were not remarkable. The nasal mucosa was slightly reddened and there was a small amount of bloody crusting in the left nostril. Examination of the mouth revealed the tongue to be quite dry. The throat appeared normal. The neck was not stiff. Examination of the lungs revealed them to be clear to percussion and auscultation. The left border dullness of the heart was percussed 9 cm. from the mid-sternal line in the fifth interspace. The apical impulse was prominent. The rhythm was regular and no murmurs were heard. On examination of the abdomen, although no organs or masses were felt, the patient's response to palpation of the left upper quadrant and left costovertebral angle indicated tenderness in those areas. Pelvic and rectal examination were negative. There was no lymphadenopathy or edema. The neurologic examination, aside from the stupor, was not remarkable.

Laboratory findings were as follows: Blood count: red cells, 3,470,000; hemoglobin, 9.7 Gm.; white cells, 5,750; differential count: stab forms, 12 per cent; segmented forms, 65 per cent; lymphocytes, 22 per cent; monocytes, 1 per cent. Urinalysis: specific gravity, 1.010; albumin, trace; sugar, negative; sediment, many white blood cells, a few in clumps, occasional red blood cell. Blood Kahn test: negative. Blood sugar: 127 mg. per cent; carbon dioxide combining power, 58.7 vol. per cent. Total protein: 5.6 Gm. per cent; albumin, 3.2 Gm. per cent; globulin, 2.4 Gm. per cent.

On admission to the hospital the patient was given 1,000 cc. of 5 per cent glucose in normal saline intravenously, and several hours later 1,000 cc. of $\frac{1}{6}$ molar sodium lactate containing 5 Gm. of sodium sulfadiazine were given intravenously. Penicillin, in a dosage of 40,000 units every three hours, was begun. On the morning following admission the patient was still obtunded; she was restless and groaned frequently. Her temperature was 40°C. She was given insulin, glucose in saline and

sulfadiazine parenterally. A blood culture which had been obtained on admission was reported to show a moderate growth of coliform organisms; the same organisms were also isolated from the urine culture. When the non-protein nitrogen was reported as 77 mg. per cent, sulfonamide therapy was discontinued and streptomycin therapy instituted. During the course of the day the patient continued to be stuporous and hyperpyrexia. A lumbar puncture was performed and the initial pressure was found to be 116 mm. of water. The fluid was clear and contained only 8 cells; the protein was 20 mg. per cent, the colloidal gold curve normal and the Wassermann negative. Further blood studies revealed the red count to be 3,640,000 with 8.7 Gm. of hemoglobin. The white cell count was 8,050, the differential showing 25 per cent stab forms, 65 per cent segmented forms, 7 per cent lymphocytes and 3 per cent monocytes. The polymorphonuclear leukocytes showed marked toxic granulation. A second blood culture obtained at this time was likewise positive for coliform bacilli. During the afternoon of the second hospital day the patient's pulse became rapid and thready. She was placed in an oxygen tent and given a whole blood transfusion. Although she continued to be stuporous, she did respond to painful stimuli. Her temperature remained at 40°C. By 5 P.M., despite administration of insulin, the blood sugar, which in the morning had been 382 mg. per cent, had risen to 443 mg. per cent. The urine sugar was 4+ and the urine was positive for acetone. The sediment showed only an occasional white cell and 3 to 5 red cells per high power field, and 1,000 cc. of $\frac{1}{6}$ molar sodium lactate was administered intravenously; 20 units of insulin was given every two hours—the urine sugar was carefully followed at frequent intervals. By 7 P.M. the blood sugar had fallen to 337 mg. per cent. By the early morning hours of the third day the urine was sugar-free.

On examination the morning of the third day the patient was still stuporous. Her

blood sugar, drawn at 8 A.M., was 211 mg. per cent. The non-protein nitrogen had risen to 80 mg. per cent. Another blood culture was drawn and subsequently was reported positive for coliform organisms. Examination of the urine at noon showed 4+ sugar, no acetone and the centrifuged sediment showed only a few white cells. Agglutination tests for typhoid were negative. During the course of the afternoon the patient's respiratory rate increased and her respirations became more shallow. Examination of the lungs was essentially negative. Re-examination of the heart revealed a grade II apical systolic murmur and an occasional ventricular premature contraction. The patient was not cyanotic but slight edema of the hands had appeared; likewise, minimal pitting over the sacrum was noted. The abdomen was moderately distended but soft. The liver did not appear to be enlarged. Tenderness in both flanks persisted; it was much more marked on the left where there was definite resistance to palpation. The kidneys could not be felt. During the course of the day constant attention was paid to the patient's diabetes which was kept under control. In addition to insulin she received a second blood transfusion and 1,000 cc. of 5 per cent glucose in water. Despite all supportive measures, however, she failed to regain consciousness and she expired at approximately 10 P.M. on February 6, 1947, the third hospital day. Her temperature had remained at approximately 40°C. throughout the last day of life.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Upon admission to the Barnes Hospital, this patient was indeed profoundly ill. She was admitted in a stuporous state and never fully regained consciousness; her condition was complicated by the presence of colon bacillus bacteremia. Dr. Schroeder, in view of the apparent localization of tenderness to the left flank and the fact that colon bacilli were recovered from both the blood and the urine, would you not agree that

the patient probably had infection of the left kidney or of the area about the left kidney?

DR. HENRY A. SCHROEDER: Yes, I should certainly think so.

DR. ALEXANDER: Do you not think it possible that the illness which occurred three years prior to admission, which was characterized by chills and fever of six weeks' duration, may have represented renal infection?

DR. SCHROEDER: That suggestion seems to me to be a good one although we have insufficient information about the episode to be certain.

DR. ALEXANDER: Would you care to suggest the lesion in the kidney? Do you believe that there was a severe enough infection to lead to renal insufficiency? As you recall the patient's non-protein nitrogen was significantly elevated.

DR. SCHROEDER: I am not sure that I can identify the pathologic lesion. The patient's blood pressure when she came to the hospital was only slightly elevated and she apparently was excreting urine satisfactorily. I believe that to explain azotemia one would have to assume that there was either previous renal damage or else the acute renal infection was bilateral and quite severe.

DR. ALEXANDER: It would seem likely to me that if elevation of the non-protein nitrogen were due to renal disease then both kidneys would have had to be involved. Dr. Futcher, do you think that the azotemia could possibly have been prerenal in origin or would you rather ascribe it to definite renal insufficiency *per se*?

DR. PALMER H. FUTCHER: I believe that there was almost certainly primary renal insufficiency, but there may have been contributing prerenal factors. The patient's diabetes apparently had not been fully controlled and she was probably dehydrated. Furthermore, in a poorly controlled diabetic there is probably increased breakdown of protein and therefore an additional amount of nitrogen to be excreted; if renal function was already impaired, this incre-

ment might assume significant proportions. Finally, on the basis of long-standing diabetes the patient may well have had intercapillary glomerulosclerosis.

DR. ALEXANDER: In other words, you believe that the patient may not have had acute infection of the kidneys alone, for example, abscesses or pyelonephritis, but that possibly she had vascular disease as well.

DR. FUTCHER: I would be inclined to think that most of the nitrogen retention resulted from the acute infection, but I believe that intercapillary glomerulosclerosis and/or pyelonephritis were probably present and of significance. Of course, there are other possible renal lesions associated with diabetes, and particularly we should mention necrotizing renal papillitis which has been described in diabetics. It occurs in association with acute pyelonephritis and is characterized by necrosis of the renal papilli. As far as I know the syndrome almost invariably leads to a fatal outcome.

DR. ALEXANDER: That is a very good suggestion. Certainly we can say that this patient's kidneys may well have been markedly involved by one of the acute disease processes mentioned. This patient, as we have noted, had bacteremia due to one of the coliform bacilli; she received large amounts of penicillin, sulfonamides and streptomycin, all apparently to no avail. Which of these agents, Dr. Harford, would you consider most effective in treating overwhelming colon bacillus infection?

DR. CARL G. HARFORD: Streptomycin would be the drug of choice in this situation. It is of interest to point out that the organism which was recovered from this patient's blood was studied and found to be sensitive to 5 micrograms of streptomycin per cc. but not to 4.

DR. ALEXANDER: You have been quoted on occasions as stating that sulfadiazine is an effective drug for the treatment of colon bacillus infection of the urinary tract. Would you comment on this point?

DR. HARFORD: There are certainly exceptions, but in many cases sulfadiazine in

adequate dosage controls such infections quite well.

DR. ALEXANDER: This patient, Dr. Wood, had had a high, unexplained fever when she first entered the hospital in her home town. Although no diagnosis was established, she was given penicillin for several days without response. At present the custom of giving chemotherapeutic agents in the presence of fever, even though a diagnosis is not established, is rather widespread. Would you comment on this practice?

DR. W. BARRY WOOD, JR.: That such a procedure may be very dangerous is illustrated by this case. It would seem to me that the physician's first responsibility is to attempt to determine the cause of the fever and to do so he should utilize all the diagnostic aids at his command. Whether one can justifiably call fever "unexplained" depends upon the effort that has been made to reach a diagnosis. In this particular case it seems in retrospect that the diagnosis of urinary tract infection might have been made more promptly and the organism isolated. Had that been done when the patient first presented herself to the outside hospital, she could have received more definitive treatment and might have made a more favorable response. We should make every effort to reach a specific diagnosis in cases of undetermined origin rather than depend upon the "shot gun" use of chemotherapeutic agents.

DR. ALEXANDER: I think your point is very well taken, but we have all seen patients whose condition was critical at the time of entry and since the results of many diagnostic procedures may not be known for several days do you think that penicillin, being the least dangerous drug, would be the agent of choice in such a situation?

DR. WOOD: I believe it is fair to say that penicillin has the widest range of application. It would probably be beneficial in more infections than would streptomycin and it is considerably more potent than the sulfonamides. Furthermore, as you have pointed out it is relatively non-toxic. How-

ever, if I were faced with the problem of treating a patient critically ill with signs of an infection in whom the specific diagnosis was unknown, I would give both penicillin and streptomycin. Had that been done promptly in the case under discussion the outcome might have been different.

DR. ALEXANDER: You would give penicillin and streptomycin but would not employ sulfonamides.

DR. WOOD: Yes. When I made the foregoing statement several days ago, Dr. Carl V. Moore correctly reminded me that there is at least one infection in which streptomycin and a sulfonamide are more effective than streptomycin and penicillin, namely, in acute brucellosis. Therefore, if one suspects undulant fever, one should probably use streptomycin and sulfadiazine; otherwise, I would tend to avoid the sulfonamides. We have discussed in these conferences during the past few years a number of fatal cases of sulfonamide intoxication.

DR. ALEXANDER: Would you comment on the use of penicillin by mouth? Is it effective by that route?

DR. WOOD: One has to give by mouth approximately five times the indicated parenteral dose to achieve the same results in terms of blood concentration. However, there are some patients who absorb penicillin poorly from the gastrointestinal tract and in such patients one often does not achieve an adequate blood level. Certainly when a patient is acutely ill, it seems much more advisable to give the drug by the parenteral route.

STUDENT: I should like to ask Dr. Wood if he thinks that sulfonamides are preferable to penicillin in the treatment of meningococcal meningitis.

DR. WOOD: Your question is a good one. I would agree that in meningococcal meningitis sulfonamide therapy is probably just as effective as penicillin; indeed, there are those who believe that it is even more effective because of its prompt diffusion into the cerebrospinal fluid. The diagnosis, however, of acute bacterial meningitis

usually is not too difficult and rarely need be considered among the "fevers of unknown origin." On the other hand, chronic meningococemia does constitute one of the causes of unexplained fever. In that instance I would prefer to use penicillin because in chronic meningococemia the focus of infection is not in the subarachnoid space but rather at a site elsewhere in the body where penicillin should be effective.

DR. ALEXANDER: To return to this case I gather that this patient actually was in a coma or in a semicomatose state for almost ten days before entry to the Barnes Hospital.

DR. JOSEPH C. EDWARDS: That is correct. I was called to see this patient in consultation at the outside hospital. At that institution there were no facilities for doing blood cultures. Our advice was that she be brought immediately to the Barnes Hospital and she was transferred without further delay.

DR. ALEXANDER: When you first saw her, did you have the impression that she was in diabetic coma?

DR. EDWARDS: Yes. In view of her history diabetic coma was one of the first diagnoses I considered, but when she failed to respond to adequate control of acidosis I assumed that there was a complicating urinary tract infection. The urinary tract involvement was suggested not so much by the urinary findings which, when I first saw her were not too striking, but rather by the physical findings which included tenderness in the left costovertebral angle. The fact that she remained obtunded despite control of her diabetes led us to consider bacteremia seriously, and for that reason a blood culture was taken immediately upon admission to this hospital. Penicillin and sulfonamide therapy were given in an attempt to combat the suspected infection, and we awaited the results of the blood culture and other laboratory data before proceeding with further treatment.

DR. ALEXANDER: When the report of the positive blood culture was made, did you think that her obtundity was due to bacteremia?

DR. EDWARDS: Not entirely. We worried about central nervous system involvement and therefore performed a lumbar puncture which, as you already know, was negative.

DR. ALEXANDER: Does the finding of normal spinal fluid exclude the presence of a brain abscess?

DR. EDWARDS: No, not in the early stage of the illness.

DR. ALEXANDER: Dr. Schroeder, do you believe that the stupor was due to uremia?

DR. SCHROEDER: No, I do not think that the non-protein nitrogen was high enough to produce coma by itself. Rather I would think that there was an additional factor, probably the bacteremia.

DR. WOOD: When I saw the patient with Dr. Edwards after her arrival in this hospital, I believed that bacteremia in itself was sufficient to explain the stuporous state. Stupor or coma may result from severe bacteremia. In addition, in this patient there were also other factors such as the uncontrolled diabetes and the urinary tract infection itself.

DR. CARL V. MOORE: I would like to ask Dr. Harford whether a pulse of 100 with a temperature of 40°C. seems entirely compatible with any of the diagnoses suggested.

DR. HARFORD: One possible explanation for bradycardia may lie in the absorption of an endotoxin elaborated by the infecting organism, a situation possibly analogous to that in typhoid fever.

DR. WOOD: I think Dr. Harford's point is very well taken. The endotoxins of various gram-negative bacilli may certainly cause bradycardia. Colon bacillus bacteremia may simulate typhoid fever; you will recall that this patient also exhibited leukopenia, common in typhoid. Bacteremia due to the *Salmonella suipestifer*, another gram-negative rod, may likewise produce a clinical picture indistinguishable from typhoid fever as was emphasized some years ago by Dr. A. M. Harvey in an excellent review of *suipestifer* infections.¹

DR. FUTCHER: In regard to the comatose

¹ HARVEY, A. M. *Salmonella suipestifer* infections in human beings. *Arch. Int. Med.*, 59: 118, 1937.

state I have seen one patient and heard of another who, in the course of treatment for diabetic acidosis, received unduly large doses of insulin and as a result developed hypoglycemia for a period of several hours. Subsequently, although the hypoglycemia was corrected, these patients failed to recover consciousness, developed hyperpyrexia and died. Is it possible that this patient's diabetes was treated over enthusiastically in the outside hospital and that the stupor was due to profound brain damage resulting from hypoglycemia? This point comes to my mind because as you will recall in the history this patient had never taken insulin prior to her admission to the outside hospital.

DR. ROBERT J. GLASER: When this patient entered the hospital, it was noted that two or three suggestive petechiae were present and examination of the heart revealed no murmurs. Subsequently, a very distinct systolic murmur of grade II intensity appeared. I wonder if she may not have developed acute bacterial endocarditis secondary to the coliform bacteremia. Since the patient's temperature was up throughout her hospital stay, development of the murmur could not be attributed to hyperpyrexia. An interval of two days is rather short for the development of such a murmur, even in acute bacterial endocarditis, but I think the diagnosis should be mentioned.

DR. ALEXANDER: I think your suggestion is a good one. The findings brought to my mind also the possibility of acute bacterial endocarditis. Dr. Smith, do you believe that this infection may have involved one of the valves?

DR. JOHN R. SMITH: I do not believe that the development of the murmur was too unusual in view of the extremely critical condition of the patient and the overwhelming infection, but I agree that the diagnosis of acute endocarditis must be considered.

DR. CYRIL M. MACBRYDE: I think that the comatose state was not due to uncontrolled diabetes but rather to severe infec-

tion. When the patient entered this hospital, her carbon dioxide combining power was essentially normal; the dehydration was corrected and the diabetes was well controlled. It must be kept in mind that occasional patients who develop severe diabetic coma remain in the coma and die even after correction of electrolyte abnormalities and control of hyperglycemia. I think hypoglycemia is quite a rare cause of death in this situation.

DR. ALEXANDER: How long may a patient survive in coma due to diabetic acidosis?

DR. MACBRYDE: Rarely over twenty-four hours if the situation is not corrected.

DR. HARTFORD: One other point in regard to the effect of bacteremia on coma may be made. Poured plates, made from blood taken on admission and on the second hospital day, showed very large numbers of organisms, but on the last day of life although the blood culture was positive the poured plates showed only a few colonies. That final culture, which was taken after twenty-four hours of streptomycin treatment, indicated that the infection was coming under control, at least as far as the blood stream was concerned and one would expect that had the stupor been due to bacteremia it should have lessened.

DR. ALEXANDER: In summary, I think we all agree that this patient probably had severe renal infection, probably acute pyelonephritis, and that possibly her kidneys were also the seat of chronic changes, among which have been mentioned intercapillary glomerulosclerosis. Necrotizing renal papillitis has been suggested as an accompanying feature of the acute pyelonephritis and finally acute bacterial endocarditis has been mentioned.

Clinical Diagnoses: Acute pyelonephritis; ? necrotizing papillitis; ? intercapillary glomerulosclerosis; ? acute bacterial endocarditis due to colon bacillus.

PATHOLOGIC DISCUSSION

DR. VOL K. PHILLIPS: At autopsy the body was that of a well developed, fairly

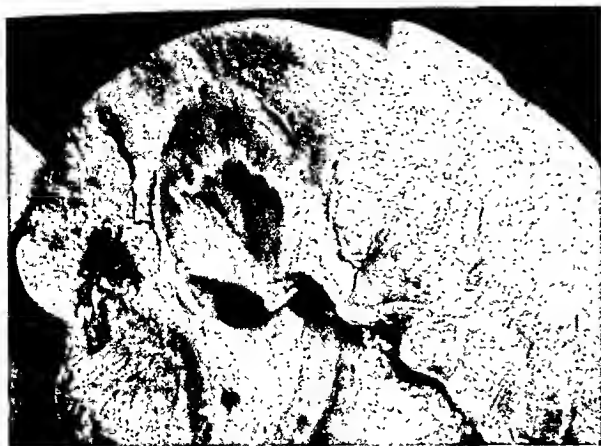
well nourished, middle-aged, white woman weighing 64 Kg. Externally there were no lesions.

The more significant findings were in the kidneys. The left kidney was greatly enlarged and weighed 440 Gm. The thin transparent capsule retracted from the cut edge and stripped easily to expose a pale red cortical surface, upon which there were numerous yellow, soft, slightly elevated foci from 1 to 4 mm. in diameter, some of which had tiny red centers. There were no scars or gross deformity. The parenchyma bulged from the cut surface and the pelvis was packed with thick, reddish-grey, purulent material. The wall of the pelvis was thickened and the mucosa was granular with numerous dilated, small blood vessels. The center of each pyramid contained a depressed, reddish-grey, firm focus, 12 to 20 mm. in diameter, surrounded by a slightly raised yellow border 1 to 2 mm. thick. Extending peripherally there were very dark purplish-red radiating lines which followed the distribution of the collecting tubules. In the inferior pole was an irregular cavity 24 by 12 by 10 mm. which was lined by a shaggy grey friable material; the cavity contained an irregular solid mass of a similarly friable substance 1 cm. in diameter. The inferior calyx led directly to this cavity which had completely replaced the renal papilla normally present in that location.

The right kidney was not as large as the left, weighing 250 Gm. It showed similar but less striking gross pathologic changes in the parenchyma, papillae and pelvis but there were neither abscesses nor completely destroyed papillae.

The urinary bladder contained a large amount of thick, reddish-grey purulent material. The mucosa was edematous and large bullae were present. Near the urethra there was a small, dark, red focus where the mucosa was inflamed and ulcerated. There was no anatomic obstruction of any part of the urinary tract.

There was clear fluid present in each pleural cavity, 500 cc. on the left and 300 cc.



1



2

FIG. 1. Gross appearance of necrotizing papillitis in the right kidney.

FIG. 2. Cavity in the lower pole of the right kidney which communicates directly with the pelvis and represents a totally destroyed renal pyramid.

on the right; in the peritoneal cavity 250 cc. of fluid were present. The serous membranes throughout the body were smooth and glistening. The liver was moderately enlarged, weighing 2,420 Gm., and was of a yellow, greasy appearance on the cut surface. The lungs and spleen were congested; the other viscera showed no pathologic lesions of major significance.

DR. ROBERT A. MOORE: We have not previously had the opportunity to present at one of these conferences a case with this highly characteristic renal lesion which occurs in association with diabetes and which is illustrated in the first two photographs of the left kidney. Figure 1 illustrates the typical lesion of necrotizing papillitis in which the central portion of a papilla is converted into grey-red tissue with linear striations which follow the normal architecture of that region of the kidney, indicating that the anatomic change had not progressed to the point where destruction of the architecture ensued. This central area is surrounded by a slightly elevated, yellow zone, varying from 1 to 2 mm. in thickness, beyond which are red streaks spreading into the surrounding pyramid. The second photograph (Fig. 2) is of the cavity in the lower pole of the kidney which at autopsy was partially filled with granular debris such as might have resulted from extension of the necrosis present in the other papillae and sloughing of the involved tissue.

Figure 3 is a slightly magnified microscopic section of a lesion similar to the one seen in Figure 1. Considered with Figure 4, which is a higher magnification of the irregular, dark line representing the narrow yellow peripheral zone seen grossly, it is apparent that the peripheral zone is a cellular region and the central zone is relatively free of cells. This lesion represents a combination of the pathologic changes which result from infection plus the occlusion of blood vessel changes leading to ischemic necrosis of tissue. In the cellular zone there is an intense inflammatory reaction with diffuse infiltration of polymorphonuclear leukocytes, many of which are undergoing necrosis themselves with karyorrhexis and karyolysis of the nuclei.

Figure 5 represents another lesion in the area of viable tissue in which there are small blood vessels filled with thrombi. These thrombi were probably produced as a result of the severe infection which seems to affect the pyramids primarily; the formation of such thrombi results in interruption of the blood supply to the entire tip of the renal pyramid. Beyond this zone there are tubules filled with polymorphonuclear leukocytes and small acute abscesses are seen in the parenchyma of the cortex.

This patient had, in addition, arteriolar disease of the kidney as is evidenced by the prominently thickened arteriole at the base of the glomerular tuft. (Fig. 6.) Although

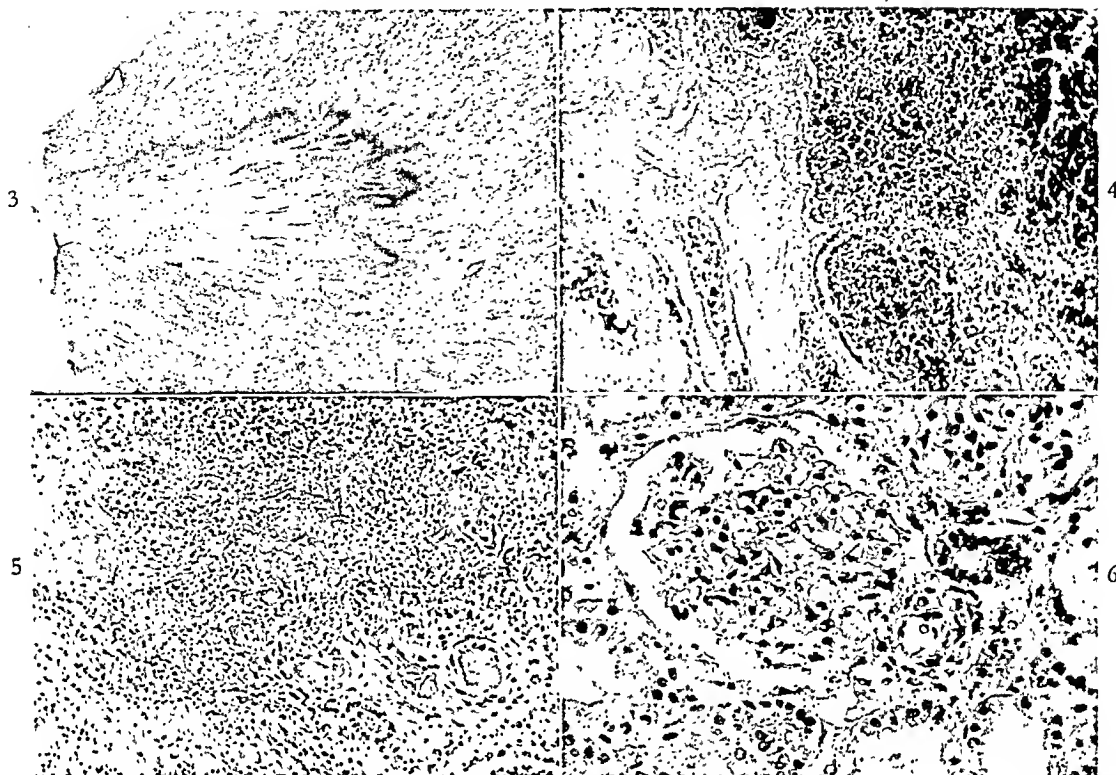


FIG. 3. Low magnification of an area of necrotizing papillitis.

FIG. 4. Moderate magnification of the edge of a necrotic papilla with the zone of ischemic necrosis to the left and the peripheral zone of cellular infiltration on the right.

FIG. 5. Peripheral zone of inflammation and thrombi in small blood vessels in an affected renal pyramid.

FIG. 6. Thickened afferent arteriole and slight thickening of the basement membrane of the capillaries in the kidney.

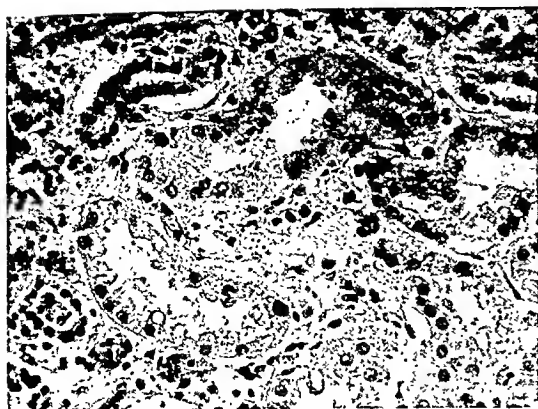
uremia is not an anatomic diagnosis, we may make observations at the time of autopsy which suggest the existence of nitrogen retention prior to death. This particular patient did not have inflammation of the serous cavities, especially pericarditis which is frequently found in uremia. Further, there was no observation at the time of autopsy that the material from the cecum had an ammoniacal odor, another of the very characteristic pathologic signs of uremia. Thickened arterioles, such as the one illustrated in Figure 6, contained foci of necrosis as though the lesions of malignant nephrosclerosis were either incipient or had just begun before death; I do not think, however, that the vascular changes had progressed as yet to the point where that diagnosis can be added.

Microscopic sections of the kidneys also showed a slight thickening of the glomerular basement membrane, again an indication

of arteriolar disease. In addition, there were occasional small deposits in the glomeruli of the dense material characteristic of intercapillary glomerulosclerosis; although this patient did have intercapillary glomerulosclerosis, I doubt that that lesion had anything to do with the terminal episode. In our experience a slight degree of intercapillary glomerulosclerosis usually gives rise to no significant clinical signs or symptoms.²

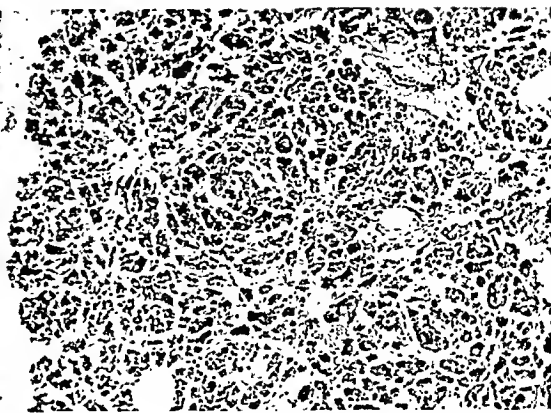
The renal tubules showed a good deal of change. Figure 7 is a fairly typical example of the proximal convoluted tubules in the kidneys; you will note that there is a great variation in the staining properties of the nuclei. The finding suggests that there had been rather severe damage to the proximal convoluted tubular epithelium for a prolonged period of time; there are some regions where no nuclei remain whereas in

² GOODP, I. I. Intercapillary glomerulosclerosis. *Ann. Int. Med.*, 22: 373, 1945.



7

FIG. 7. Proximal convoluted renal tubules with variable intensity of staining. There are some foci in which there has been loss of nuclei and others in which nuclei have accumulated, indicating beginning regeneration.



8

FIG. 8. Slight diffuse interstitial fibrosis in the pancreas.

others there is an accumulation of nuclei indicative of beginning regeneration.

The anatomic lesions in the pancreas which might be attributed to diabetes were not very striking. Figure 8 illustrates the fairly typical example of slight interstitial fibrosis which was present. The islets are for the most part fairly well preserved and only in a few areas are single hyaline islet cells seen. The arteriolar changes in the pancreas were striking; many vessels had walls which were about twice as thick as normal and completely hyalinized.

In summary, this patient had a very characteristic lesion which is seen in the kidney in some cases of diabetes. From the anatomic standpoint it is the result of a severe, rapidly progressing infection which produces occlusion of blood vessels and leads to the secondary changes of ischemic necrosis in the renal papillae. The lesion

and its associations with diabetes has been emphasized in the literature, principally during the past few years, and the paper of Edmondson et al.³ may be consulted for further study.

Anatomic Diagnoses: Acute pyelonephritis with abscess formation, left severe, right moderate; *Escherichia coli* cultured from the heart's blood and the renal pelvis; necrotizing papillitis, left kidney severe, right moderate; acute cystitis; arteriolar nephrosclerosis; intercapillary glomerulosclerosis, slight; arteriosclerosis, generalized, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University of Medicine.

³ EDMONDSON, H. A., MARTIN, H. A. and EVANS, N. Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus. *Arch. Int. Med.*, 79: 148, 1947.

Case Reports

Acute Endocarditis Due to Staphylococcus Aureus Successfully Treated with Penicillin*

C. MAYNARD GUEST, M.D. *and* FRANCIS F. HARRISON
New York, New York *Cooperstown, New York*

THE successful treatment of endocarditis due to Staphylococcus aureus with penicillin is still unusual as is evidenced by the fact that we were able to find only twelve such cases in the literature. These cases, as well as the one which we are reporting, are summarized in Table I.

102°F., malaise, chilly sensations, nausea, vomiting and diarrhea. In the course of the next four days the gastrointestinal symptoms largely subsided, to be replaced by coryza, sore throat and a cough productive of mucoid sputum. Her fever rose to 104°F. She was given penicillin, 15,000 units intramuscularly, every three hours for the next two days, but in spite of this her temperature continued at a high

TABLE I
RESUMÉ OF CASES REPORTED IN THE LITERATURE

Author	Daily Dose Penicillin x 1 Million Units	Route	Days Treated	Total Penicillin x 1 Million Units	Results
Dolphin ¹	0.048-0.12	IM	36	2.1	well, 12 mo.*†
Glaser ²	0.36	IV	13	4.7	well, 21 mo.
Glaser.....	0.04-0.3	IV, IM	26	3.1	well, 20 mo.
Glaser.....	0.2-1.2	IM	22	11.6	well, 10 mo.
Glaser.....	0.24-1.2	IV, IM	67	58.6	well, 1½ mo.
Harford ³	IV, IM	13	4.9	well, 4 mo.*
Harford.....	IV, IM	25	3.2	well, 2 mo.*
Harris ⁴	0.045-0.4	IM	46	6.3	well, 7 mo.*†
Howells ⁵	0.32	IM	9	3.0	well, 1 mo.*
Hoyt ⁶	0.12	IM	14	1.7	well, 18 mo.*
MacNeal ⁷	0.0072-0.12	IM	62	3.7	well, 11 mo.†‡
Wilhelm ⁸	0.2-2.0	IM	56	13.4	well, 20 mo.*
Guest and Harrison.....	1.04	IV, IM	43	44.6	well, 32 mo.

IV, intravenously; IM intramuscularly.
* Sulfonamide also given.
† Penicillin given intermittently in three or more courses.
‡ Staph. aureus bacteriophage, thiobismol and neoarsphenamine also given.

CASE REPORT

H. B., a twenty-two year old white female, was admitted to the Bassett Hospital on December 9, 1945. At the age of fourteen she had had chorea and four years later a heart murmur was first noted. The present illness began abruptly fifteen days before admission, with fever of

level, her shoulder joints became tender and painful and there was syncope on one occasion. Eight days before admission she entered another hospital where a tentative diagnosis of acute rheumatic fever was made, for which she received 4 to 6 Gm. of aspirin daily for the next four days. Four days before admission the patient became jaundiced and petechiae were

noted on the toes and in the conjunctivae. A blood culture taken on this day was subsequently reported positive for a gram-positive coccil organism. On each of the last two days before admission she received an infusion containing 200,000 units of penicillin. Despite this she became confused and lethargic and her temperature rose to 105°F.

Physical examination on admission revealed that the temperature (rectal) was 101.2°F., pulse rate 60, respiratory rate 26, blood pressure 105/62 and weight 120 pounds. The patient appeared acutely ill, dyspneic and drowsy. The skin was hot, dry and icteric. There were petechiae on the conjunctivae, soft palate and left tonsillar fossa, a round retinal hemorrhage was present, and a tender, hemorrhagic lesion was visible on the fourth right toe. On the extremities there were scattered, dull red macules, 4 to 6 mm. in diameter, which blanched with pressure. There was a pustule on the left leg. The tip of the third right finger, pricked for a blood count before admission, appeared infected. Cardiac dullness extended just beyond the mid-clavicular line in the left fifth interspace. The rhythm was regular. There were loud apical and basal systolic murmurs as well as a blowing diastolic murmur along the left sternal border which was loudest in the third interspace. The spleen was palpable and tender. The lungs were clear, the liver was not enlarged, the neck veins were not engorged, there was no cyanosis, no dependent edema and no evidence of meningeal irritation.

Laboratory studies revealed the following: The hemoglobin was 11.3 Gm. and the white blood count was 9,000 with 84 per cent neutrophils. The erythrocyte sedimentation rate (Wintrobe's method, uncorrected) was 49 mm. fall in one hour. The icterus index was 14. A blood culture was positive for *Staphylococcus aureus* hemolyticus, coagulase positive. The colony count was 227 per cc. of blood. A culture of the pustule on the left leg was positive for a similar organism. The micro-organism from the blood culture grew in a concentration of 0.06 units of penicillin per cc. and was inhibited by a concentration of 0.125 units (Kolmer's method). It was also inhibited by 10 mg. per cent of sulfathiazole. A catheterized urine specimen showed 1 plus albumin, 2 to 4 red blood cells per high power field, and from it *Staphylococcus albus* and coliform bacilli were cultured. An

electrocardiogram was normal. A portable chest x-ray showed probable cardiac enlargement.

The course in the hospital (shown in the accompanying illustration) was stormy. On the second hospital day the patient became semi-comatose, her temperature rose to 106.6°F., the pulse rate to 130 and the respiratory rate to 50. There were many crackling râles at both lung bases and a gallop rhythm developed. A continuous infusion of penicillin, 800,000 units in each twenty-four-hour period, together with intramuscular injections of 80,000 units every eight hours, were started and continued for forty-three days. Oxygen was administered by nasal catheter for the first eight hospital days. The hemoglobin rose from a low of 9.9 to 14.7 Gm. after five small blood transfusions were given during the first hospital week. There was no subsequent anemia. Although the spiking fever and rapid pulse were slow in abating, the patient's appearance rapidly improved during the first ten days. She became mentally alert. Dyspnea, icterus and gallop rhythm disappeared. The spleen was not palpable at the end of the second hospital week. Nevertheless, a positive blood culture in three of five flasks was obtained on the fourteenth hospital day. Because of this and because the microorganism was moderately sensitive to sulfathiazole, this drug was given from the nineteenth to the sixtieth hospital days (total dosage was 234 Gm.). Intermittent microscopic hematuria continued until the twentieth hospital day. No peripheral embolic phenomena were noted from the twentieth to the thirty-second hospital day when an Osler's node appeared on the left hand. Two weeks later she was ambulatory and was discharged on the sixty-sixth hospital day.

An inconstant, soft, low pitched, apical diastolic murmur was heard during her hospitalization. The basal diastolic murmur became louder but the systolic murmurs decreased in intensity. Her blood pressure averaged about 110/75. After the first hospital week there were no signs of cardiac failure. X-rays showed a 15 per cent increase in the cardiac size (as estimated by the Ungerleider table). The cardiac silhouette was not diagnostic of any particular valvular lesion.

The patient has been followed for fifteen months and there has been no evidence of recurrence. Six blood cultures have been negative. The erythrocyte sedimentation rate has been within normal limits. The basal diastolic murmur has persisted unchanged but the basal

systolic murmur has disappeared and the apical systolic murmur has become less pronounced. There has been no evidence of cardiac failure and the cardiac silhouette, as seen in x-ray examinations, has remained unchanged. Her activities were gradually increased and for the last eight months she has been able to carry on her duties as a school teacher.

COMMENT

The most notable feature of the available reports on the treatment of Staph. aureus endocarditis with penicillin is the low dosage as compared to present day practice. This may well be an important factor in the cause of the previous high mortality in penicillin-treated patients inasmuch as these patients are likely to die rapidly of overwhelming infection. To be sure one is usually dealing with an organism relatively sensitive to penicillin, yet our patient had one positive blood culture after receiving 12 million units of the drug, an amount greater than the total dosage of all but two of the previously reported cases. In our patient therapy was delayed for some hours in order to establish an accurate bacteriologic diagnosis. In retrospect we doubt that this delay was justifiable. We also believe that our dosage schedule, thought at the time to be high, should now be regarded as minimal.

SUMMARY

1. The previously reported cases of those with Staph. aureus endocarditis who were

treated successfully with penicillin, together with one of our own, are tabulated.

2. Suggestions are made regarding the therapeutic approach to this disease.

ADDENDUM

On November 9, 1948, thirty-two months after discharge from the hospital, the patient's private physician informed me that she is married and well.

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A Case of Infectious Mononucleosis with Jaundice and Thrombocytopenic Purpura*

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THE protean manifestations of infectious mononucleosis and the varied conditions which it may simulate are well known to all. Jaundice was only rarely encountered in infectious mononucleosis¹ until World War II.² In contrast

headache, anorexia and vomiting developed. The day before admission the patient noticed that his stools were clay-colored. On the morning of admission he awoke from sleep with marked bleeding from the gums, epistaxis and hematemesis. He also noticed large ecchymotic areas and smaller purpuric spots on both thighs.

TABLE 1
URINARY FINDINGS

Date	Albumin	Bile	Urobilin	Urobilinogen	R.B.C.
February 28	Trace	+	90-100
March 1	+	..	+
March 2	+	..	+
March 3	0	2-3

to the many reports of jaundice complicating infectious mononucleosis in military personnel during the war no cases of thrombocytopenic purpura were mentioned.³ To date very few such cases can be found in the literature.⁴⁻⁶ Because of the rarity of the combination of thrombocytopenic purpura and jaundice as complicating conditions in infectious mononucleosis, and to stress the fact that the presence of mild jaundice indicates the benign character of purpura hemorrhagica, the following case is considered worthy of report.

CASE REPORT

R. H., a white male aged twenty-one, was admitted to Beth Israel Hospital on February 28, 1946. The past history was irrelevant. A week before admission the patient was seized with general malaise and a "grippy" feeling. At the onset the temperature was 103°F. The fever declined rapidly but two days later severe

Upon first examination the patient was found to be mildly jaundiced. This was overshadowed by the predominant clinical finding of hemorrhagic diathesis such as marked epistaxis, requiring packing of the nose, and excessive bleeding from soft, spongy gums. Upon taking the blood pressure diffuse areas of purpura (Rumpel-Leede phenomenon) were produced. No glands were palpable nor could the spleen be felt. The blood pressure was 110 systolic and 70 diastolic. The pulse was 63. The clinical picture the first day of admission resembled acute leukemia or thrombocytopenic purpura. The urine showed a trace of albumin; 1 plus bile and urobilinogen and 90 to 100 red blood cells which gradually returned to normal. (Table 1.)

The peripheral blood findings are tabulated in Table II. It is seen that there was no anemia, the hemoglobin and red blood cells being normal. There was a tendency to leukopenia with a shift to the left. The increased and abnormal lymphocytes were of the type most commonly seen in acute infectious mononucleosis. The platelets

* From the Medical Service of the Beth Israel Hospital, New York, N. Y.

were considerably diminished. A bone marrow study showed no abnormality. (Table III.) Megakaryocytes were present in low, normal numbers and not greatly increased as in the usual case of idiopathic thrombocytopenic purpura. This low megakaryocyte level sug-

In addition to the purpura hemorrhagica, hepatitis was undoubtedly present as shown by the jaundice, direct van den Bergh reaction, a positive Hanger cephalin flocculation test and low cholesterol and cholesterol esters. (Table IV.)

During the patient's stay in the hospital (ten

TABLE II
PERIPHERAL BLOOD FINDINGS

Date	R.B.C. (million)	Hemo- globin %	Hemo- globin Gm.	W.B.C.	Bands	Seg- ments	Baso- philes	Eosino- philes	Lym- phocytes	Mono- cytes	Platelets
February 28	5.10	97	15	7,800	19	22	50	9	
March 1	4.98	101	17	4,800	6	37	1	3	37	6	30,600
March 2	5.00	91	14	7,500	5	61	..	1	24	7	35,000
March 5	4.56	91	14	7,250	6	57	1	3	30	5	296,400
March 10	5.25	103	18	8,350	4	46	..	5	45	0	
October 1	4.10	92	15	8,000	..	60	..	1	32	7	

TABLE III
STERNAL BONE MARROW PUNCTURE

Nucleated cells, 35,000
Megakaryocytes, 22
Myeloblasts, 2 per cent
Promyelocytes, neutrophiles, 4 per cent
Myelocytes, neutrophiles, 39 per cent
Eosinophiles, 1 per cent
Non-segmented polymorphonuclears, 16 per cent
Segmented polymorphonuclears, 3 per cent
Segmented polymorphonuclear eosinophiles, 1 per cent
Plasma cells, 2 per cent
Hematogones, 3 per cent
Lymphocytes, 10 per cent
Erythroblasts, 5 per cent
Normoblasts, 14 per cent

days) the temperature was not elevated and there was a gradual recession of the purpura and icterus.

COMMENT

In view of the onset with diffuse bleeding the possibility of acute leukemia had to be considered. This was ruled out by the absence of enlarged lymph nodes, spleen, or leukemic cells in the bone marrow. The normal bone marrow also ruled out true thrombocytopenic purpura. The diagnostic

TABLE IV
LIVER FUNCTION STUDIES

Date	Icteric Index	van den Bergh	Bilirubin (mg. %)	Serum Protein (Gm. %)	Albumin (Gm. %)	Globulin (Gm. %)	Chol- esterol (Mg. %)	Chol- esterol (Mg. %)	Cephalin Flocculation Test (24-48 hr.)	
March 1	27.6	direct prompt	6.1	114	..	+++	++++
March 6	25.6	5.7	3.9	1.8				
March 8	12.5	138	40		
March 10	10.1	6.7	5.1	1.6	0	+
October 1	0	0

gested some defect in fragmentation of the platelets connected with an unusual reaction of the bone marrow which would diminish as the infection cleared up.

problem in this case was to correlate the three outstanding clinical findings: jaundice, purpura and the peripheral blood picture of infectious mononucleosis. Were we deal-

ing with infectious mononucleosis complicated by hepatitis and thrombocytopenic purpura or with infectious hepatitis with the blood picture of leukopenia, mononucleosis, lymphocytosis and the added complication of thrombocytopenic purpura?

As illustrated in the case the differentiation between infectious hepatitis and infectious mononucleosis complicated by jaundice is often difficult. The mechanism of the production of jaundice in cases of infectious mononucleosis is not definitely established

TABLE V
BLOOD STUDIES

Date	Coagulation Time	Bleeding Time	Sedimentation Rate (mm.)	Prothrombin Times		Heterophile Reaction
				Whole (Sec.)	Dilute (Sec.)	
March 1	3'50"	10'30"	0
March 6	2'30"	3'50"	12	16.85	35.85	..
March 10	3	0

If purpura were not present in this case, the clinical picture would be more that of infectious hepatitis than of infectious mononucleosis. The onset of the disease with general malaise and grippy sensation is quite characteristic of hepatitis as well as the degree of jaundice and signs of liver damage. The blood picture of leukopenia, mononucleosis and lymphocytosis suggested the diagnosis of infectious mononucleosis. It should be noted, however, that this same blood picture may also be seen in the early stages of infectious hepatitis as recently demonstrated by Havens and Marek⁸ in experimentally produced virus hepatitis in human volunteers. The absence of a positive Paul-Bunnell heterophile reaction does not preclude the diagnosis of infectious mononucleosis as reported by several investigators.^{9,10}

Purpura is not encountered in infectious hepatitis except in a severely toxic case or one of acute yellow atrophy. In infectious mononucleosis, however, although thrombocytopenic purpura is an extremely rare complication, it does occur but is not of serious prognostic import, being seen even in milder cases. Considering the short duration of the bleeding diathesis in this patient, we believe the most suitable diagnosis is acute infectious mononucleosis with complicating hepatitis and thrombocytopenic purpura.

yet. There are two schools of thought: one believes that the jaundice is due to enlarged lymph nodes pressing mechanically on the bile ducts;¹¹ the newer belief is that it is a direct toxic action upon the liver itself.¹²

As for the production of purpura in infectious mononucleosis, Dameshek and Grassi¹³ believe that it is due to a state of hypersplenism in which the spleen not only depresses the formation and delivery of megakaryocytes and platelets but causes a reduced delivery of neutrophils from the bone marrow and thus results in lymphocytosis. Lloyd⁴ believes it is the vascular damage secondary to acute infection together with a loss of circulating platelets at the purpuric site that causes the hemorrhagic phenomena. The low platelet count in the circulating blood may be the expression of a transient toxic effect exerted peripherally rather than centrally.

SUMMARY

A case of infectious mononucleosis with complicating jaundice and thrombocytopenic purpura is presented because of its rarity. The hemorrhagic phenomena of epistaxis, hematemesis, bleeding gums and petechiae simulated true thrombocytopenic purpura. However, the presence of a blood picture typical of infectious mononucleosis indicated a favorable prognosis which was

vindicated by the short duration of the hemorrhagic diathesis. The mechanisms of the production of the jaundice and thrombocytopenic purpura in infectious mononucleosis are discussed.

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Thrombophlebitis Migrans with Involvement of Both Lateral Sinuses

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ALTHOUGH lateral sinus thrombosis is not an uncommon complication of mastoid infection, instances of bilateral thrombosis are rare. Rarer still are lateral sinus thromboses of non-otitic origin. No parallel could be found in the literature to the case herein described of benign bilateral thrombosis from thrombophlebitis migrans.

CASE REPORT

J. B., a Jewish lawyer aged twenty-nine, was referred to the Sixth General Hospital by his physician, with the complaint of progressive loss of vision. He was first seen in mid-December, 1943. Loss of vision began insidiously seven months before and was accompanied at first by a moderately severe vertical headache. The headache subsided spontaneously in a few months but the loss of vision continued.

The patient was suspected of having a brain tumor because in addition to these complaints he was found to have papilledema, optic atrophy and a very high cerebrospinal fluid pressure.

The only element of note in the past history was the presence of migratory phlebitis of the lower extremities during the preceding seven years. A small segment of vein would become reddened, firm, somewhat tender and then subside to a painless area of induration. No treatment had been of avail and gradually all the veins of the legs and part of the thighs had become involved. Recently there had been an extension of the process to the upper extremities, neck and head.

Upon physical examination the patient was a slender, swarthy, well nourished man. There was chronic, non-pitting, woody edema from the ankles to the knees, with a mottled bluish discoloration of the overlying skin. No ulcerations or scars were noted. The temperature and arterial pulsations of the extremities were normal. A portion of the right frontal and angular

veins was firm, cylindric, non-collapsible and reddened but non-tender. The left external jugular vein was similarly thrombosed through the upper half of its course. The lower portion could be distended by supraclavicular pressure and collapsed by its release.

The temperature, respirations, pulse rate and blood pressure were normal. Examination of the heart, lungs, abdomen and lymph nodes showed no abnormalities.

Neurologic examination was entirely negative except for the eyegrounds. The detailed report has been unfortunately lost in military transit but it is recalled that the visual acuity was approximately 20/70 in each eye, and perimetry revealed enlargement of the blind spots. There was about 1 diopter elevation of the right optic disc and somewhat less of the left. Both were very pale, although not chalk-white, and the margins were blurred. Engorgement of the veins and one or two resorbing hemorrhages were noted. The findings were considered typical of secondary optic atrophy from chronic papilledema.

Complete hematologic, urine and stool studies were done, with only a single abnormality noted: a persistent eosinophilia of 6 to 8 per cent. The Kahn test was negative as were repeated searches for parasites in the blood, urine and stools. The patient was even examined after 10 P.M. on one occasion for microfilariae. Inasmuch as most Moroccans and, indeed, most American soldiers in Morocco showed a similar degree of eosinophilia in routine laboratory investigations without any discoverable trace of parasitism, this finding was discounted. The absence of pain and the duration of symptoms were inconsistent with trichiniasis. Repeated blood cultures on routine and special media were negative.

On December 31, 1943, the patient appeared with a fresh 2 cm. area of reddening and swelling on the radial aspect of the right wrist. A portion

of the nodule was excised and fixed. Histologic examination showed a section of vein containing a completely occluding adherent thrombus. Mild inflammatory changes were found in the vein wall and adventitia.

Roentgenograms of the skull and chest were within normal limits. Cerebrospinal fluid was examined on two occasions and found to be entirely normal as to cytology, chemical components and the Wassermann test. The sole abnormality, confirming the referring physician, was a pressure each time in excess of 700 mm. of water and a positive Tobey-Ayer test¹ on either side.

A brain tumor was considered unlikely in view of complete absence of localizing signs, normal spinal fluid protein, spontaneous subsidence of the headache and negative skull films. On the other hand, a unitary diagnosis was suggested by the cephalic involvement with thrombophlebitis migrans and the bilaterally positive Tobey-Ayer test: extension of the thrombophlebitis into both lateral sinuses with consequent hydrocephalus and papilledema.

The patient was placed on full doses of sulfadiazine (4 Gm. initially and 1 Gm. every four hours) for a period of two weeks. No change in his condition was noted. Penicillin was not available.

A recent letter from his physician (three and one-half years later) states that the patient is well but gives no details.

COMMENTS

Frequency of Bilateral Thrombosis of Lateral Sinuses. Prior to this report only fifteen other cases of bilateral thrombosis of the lateral sinuses could be found recorded in the literature. The last complete review is that of Smith² in 1939. He collected ten cases from other reports and added one of his own. All were of otitic origin and all the patients recovered. Three were treated by ligation of both internal jugular veins and seven with ligation of only one. One recovered without ligation. Irish,³ in a study of 12,000 consecutive necropsies, found three cases, two otitic and one from a posterior neck abscess. One case was added by Brownell⁴ and one by Brown and Bowman.⁵ Both were otitic and both patients died.

The writer has reviewed 12,000 consecutive necropsies at the Massachusetts General Hospital and found four more. Two were otitic, a third was an unsuspected finding in a sixty-five year old man dying of bronchopneumonia and pontine softening and the fourth occurred together with meningitis following removal of a melanotic sarcoma of the neck. This brings the total to twenty cases. The fact that nine of the twenty patients succumbed points to the seriousness of this complication. There is reason to believe that the condition occurs more commonly than the figures indicate. Authors tend to report only the cases that recover. Careful search of any large autopsy series should turn up a few instances. Even the autopsy figures are not correct for pathologists do not routinely examine the skull.

Clinical Effects of Bilateral Sinus Occlusion. Hastings⁶ discusses bilateral internal jugular vein ligation in such conditions as tuberculous lymphadenitis, cancer of the pharynx and metastatic carcinoma. Among the effects noted were convulsive seizures, marked cyanosis and no effect. In Smith's² case bilateral thrombosis with ligation of one jugular vein was associated with papilledema and a cerebrospinal fluid pressure of 460 mm. of water. The patient was well after three years.

The Nature of Phlebitis (or Thrombophlebitis) Migrans. This condition is described under both these names. Thrombophlebitis is more accurately descriptive and the other name should be dropped. Homans⁷ describes it as a true disease of the vein wall, occasionally in individuals with normal clotting tendency. It occupies a short length of vein wall, usually on an extremity. There is little tendency to embolism (this statement is denied by other authors.) Attempts have been made to link thrombophlebitis migrans to Buerger's disease (Thromboangiitis obliterans).⁸ Swirsky and Cassano⁹ describe it as an uncommon condition of unknown etiology involving chiefly the superficial veins of the extremities. Visceral organs are rarely involved. The course is variable and

usually benign. Up to 1943 there were only about one hundred reported cases with five acceptable autopsies.

Collateral Circulation. According to Gray's Anatomy¹⁰ the following are the main anastomotic connections through which the great sinuses may drain into the systemic venous system when both lateral sinuses are occluded: (1) pterygoid plexus (via middle meningeals and cavernous sinuses); (2) occipital vein (via the parietal emissary vein); (3) inferior petrosal sinus (joins superior bulb of internal jugular and is blocked when internal jugular is ligated or thrombus extends down to the bulb); (4) pharyngeal veins (via posterior meningeals); (5) vertebral vein (via vein of the condyloid canal, internal vertebral venous plexuses and occipital and basilar sinuses); (6) diploic veins (via meningeal and pericranial connections); (7) the ophthalmic veins; (8) nine groups of emissary veins some of which were first mentioned. There are many accessory connections.

SUMMARY

An instance of thrombophlebitis migrans verified by histologic study is presented.

The patient suffered thrombosis of both lateral sinuses from cephalic extension of the disease, a complication previously unreported. He recovered.

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AUTHOR INDEX VOLUME V

- Allison, James B., 419
 Ayvazian, L. Fred, 470
- Baldwin, Eleanor de F., 792
 Bartels, Elmer C., 48
 Bassett, Samuel H., 518
 Beck, Gustav J., 462
 Bellet, Samuel, 838
 Bennett, Ivan L., Jr., 729
 Björkenheim, Gösta, 807
 Bland, John H., 298
 Blumgart, Herrman L., 321
 Boisvert, Paul J., 24
 Brenner, Joel J., 288
 Bryner, Sergius, 202
- Canter, Harry Ellis, 780
 Chambers, William N., 308
 Clark, E. Gurney, 655
 Clark, William H., 202
 Clarke, Delphine H., 188
 Cohen, Ephraim B., 44
 Cuthbertson, D. P., 879
- Dattner, Bernhard, 709
 Davis, Helen P., 44
 Donegan, Charles K., 304
 Drake, William L., Jr., 775
 Draper, Arthur J., 59
 Draper, George, 165
- Eagle, Harry, 629
 Elman, Robert, 760
- Fisher, Ralph Lee, 503
 Friedman, Harold A., 518
 Frisk, A. Rune, 807
- Gellhorn, Alfred, 496
 Gladstone, Sidney A., 849
 Goldbloom, A. Allen, 912
 Goldenberg, Marcel, 792
 Goldman, Melvin L., 33
 Gordon, Burgess, 853
 Graef, Irving, 188
 Grayzel, David M., 252, 570
 Greene, David G., 792
 Guest, C. Maynard, 908
 Gutman, Alexander B., 1
- Hagemann, Paul O., 237
 Hammarström, Sven, 807
 Hare, Laura, 53
 Harrington, William J., 40
 Harrison, Francis F., 908
 Heller, J. R., 629
 Heyman, Albert, 729
 Hochstein, Elliott, 288
- Holley, Howard L., 561
 Hollis, W. J., 138
 Holmgren, Alf, 807
 Holoubek, J. E., 138
 Homburger, F., 264
 Horger, Eugene L., 821
 Hyman, Albert Salisbury, 351
- Ingraham, Norman R., Jr., 693
- Jacobsen, Victor C., 148
 John, Henry J., 537
- Kaylor, Cornelius T., 324
 Keutmann, E. Henry, 518
 Kirsner, Joseph B., 69, 230
 Kochakian, Charles D., 518
- Lagerlöf, Henrik, 807
 Lang, Leonard P., 853
 Lanning, Mary, 838
 Larsson, Yngve, 807
 Lattimer, John Kingsley, 256
 Lazarus, Joseph A., 76
 Leff, William A., 288
 Lehman, William L., 482, 496
 Liebersen, Abraham, 912
 Littman, David, 337
- Magnuson, Harold J., 641
 Maimon, Samuel N., 230
 Massey, Franklin C., 775
 Mathews, W. R., 138
 McGavack, Thomas Hodgce, 90
 Mead, Sedgwick, 916
 Messer, Addison L., 304
 Meyer, Karl, 482, 496
 Moister, F. Corbin, 308
 Moloney, William C., 40
 Motley, Hurley L., 853
 Mowry, William A., 44
 Murphy, Albert S., 40
 Murphy, Francis D., 574
- Nadler, Carl S., 838
 Neurath, Hans, 670
 Newman, Robert Carl, 574
- Orgain, Edward S., 304
- Palmer, Walter Lincoln, 230, 479
 Peirce, Charlotte T., 716
 Peters, Bruno J., 574
 Peters, John P., 100
 Phillips, Harry S., 167
 Pierson, Gray, 561
 Pines, Kermit L., 792
 Prudden, John F., 482, 496
- Raginsky, Bernard B., 857
 Ralli, Elaine P., 188
 Randall, Elizabeth, 3, 202
 Rantz, Helen H., 3
 Rantz, Lowell A., 3, 24, 202
 Reynolds, Frank W., 679
 Ricketts, William E., 69
 Rinzler, Seymour H., 736
 Robb, Jane Sands, 324
 Roh, Charles E., 792
 Rosahn, Paul D., 631
 Rosenberg, Benjamin, 462, 815
 Rosenberg, Charles A., 143
 Rosenbluth, Milton B., 815
 Rosenthal, Alfred E., 815
 Rosenthal, Julius, 462
 Rothman, Stephan, 69
 Rubin, Saul H., 188
 Russ, Ella M., 518
 Rytand, David A., 548
- Schroeder, Henry A., 33
 Schwarz, Lewis H., 76
 Shepard, Edward M., 821
 Shorr, Ephraim, 783
 Smedal, Magnus I., 210
 Sokolow, Maurice, 365
 Solomon, Harry C., 712
 Spatt, Samuel D., 252, 570
 Steinberg, Anita, 482, 496
 Stewart, Harold J., 821
 Stine, Leonard A., 610
 Straus, Bernard, 245
 Stueck, George H., Jr., 188
 Swank, Roy Laver, 210
 Swarts, Jerome M., 610
 Szilagyi, Nelly, 379, 392
- Tarail, Robert, 828
 Taran, Leo M., 379, 392
 Thomas, Evan W., 687
 Tillman, Alvin J. B., 167
 Tucker, Harold A., 702
 Turman, William G., 324
- Waring, Geo. W., Jr., 402
 Weinstein, Louis, 402
 Werkö, Lars, 807
 Werner, Sidney C., 749
 Wilder, Russell M., 532
 Wilmore, Ralph, 53
 Wolfe, Joseph B., 87
 Wooldridge, Wilfred E., 237
- Young, Nelson F., 586
- Zahn, Daniel W., 716
 Zukerman, Morris, 503

SUBJECT INDEX VOLUME V

(E.) = Editorial

Abstracts of papers of American Federation for Clinical Research, 157, 311, 616

Acidosis, diabetic, electrocardiogram in, 838

Agranulocytosis and propylthiouracil, 48

Allergy, thephorin in, 44

American Federation for Clinical Research, 157, 311, 616

Amino acids

as parenteral protein food, 760

pure, and protein hydrolysates, 879

Androgens in Cushing's syndrome, 518

Antistreptolysin "O," 3

Antithyroid substances in thyroid disease, 90

Anuria, fatal, 548

Atelectasis, pulmonary, 210

Bacteremia, hemolytic staphylococcus albus, and pericarditis, 298

Biopsy, sponge, in cancer diagnosis, 849

Blood pressure, arterial, effect of diets on, 815

Book reviews

A Manual of Pharmacology (Sollmann), 628

Cornell Conferences on Therapy (Gold), 782

Engrammes of Psychiatry (Nielsen and Thompson), 628

Pathology of Nutritional Disease (Follis), 478

Unipolar Lead Electrocardiography (Goldberger), 478

Bromsulfalein reaction, 308

Bundle branch block during an electrocardiogram, 780

Calculi, urinary, 256

Cancer

diagnosis, sponge biopsy in, 849

gastric, prognosis in, 230

Carcinoma of liver, 561, 570

Carcinoma of lung, deep x-ray in, 148

Cardiac rhythm, management of disorders of, 110

Cardiac pain, 736

Chest, acute pain of, 599

Cirrhosis of liver, 188

Clinic on psychosomatic problems (Massachusetts General Hosp.)

A case of hysteria, 272

Fecble-mindedness or pseudoretardation, 891

Clinico-pathologic conferences (Washington Univ.)

Acute, severe chest pain with fatal termination, 599

Diabetes, fever of unknown origin and coma, 898

Obesity, hypertension, diabetes and heart failure, 277

Pneumococcal meningitis, 449

Progressive congestive heart failure with peripheral vascular collapse, 126

Colitis

ulcerative, and Pyoderma gangrenosum, 69
lysozyme in, 496

Columbia combined staff clinics

Peripheral vascular disease, 433

Coma, fever and diabetes, 898

Combined staff clinics (Columbia Univ.)

Peripheral vascular disease, 433

Conferences on therapy (Cornell Univ.)

Management of disorders of cardiac rhythm, 110

Therapeutic uses of gamma globulin, 590

Convalescence, problems of (E.), 165

Cornell conferences

Management of disorders of cardiac rhythm, 110

Therapeutic uses of gamma globulin, 590

Cor pulmonale, 252

Coronary arteries as end arteries (E.), 321

Coronary artery disease in dextrocardia, 304

Cushing's syndrome, 518

Dermatitis of poison oak, 548

Desoxycorticosterone acetate, pressor effect of, in arterial hypertension, 33

Dextrocardia, congenital, 304

Diabetes, 277

and Friedländer bacillus meningitis, 470

fever and coma, 898

mellitus, and visceral neuropathy, 610

treatment of, 537

Dicumarol, prolongation of coagulation of whole blood with, 40

Electrocardiograms

abnormal, 337

in diabetic acidosis, 838

Electrocardiography

changes in rheumatic fever, 365

disturbances and abnormalities of serum potassium, 828

manifestations of potassium intoxication, 821

Embolism, pulmonary, and venous thrombosis, 716

Emphysema, mediastinal, and pneumothorax, 59

Endocarditis

acute, treated with penicillin, 908

subacute bacterial, 143

renal excretion of penicillin in, 202

Enteric coating, value of, 87

Epidemiology of syphilis, 655

Epinephrine, nor-epinephrine and hypertension, 792

Feeble-mindedness or pseudoretardation, 891
Fever, coma and diabetes, 898
Fibrinolysin streptococcal, 24
Friedländer bacillus meningitis and streptomycin, 470

Gastric cancer, prognosis in, 230
Gaucher's disease, 245
Globulin, gamma, uses of, 590
Granuloma, eosinophilic, 245

Heart
 disease, abnormal electrocardiograms in absence of, 337
 asymptomatic, 351
 failure, 277
 congestive, and peripheral vascular collapse, 126
 fetal, study of tissues of, 324
 spontaneous rupture of, 775
Hepatitis, thiouracil, 138
Histiocytosis, metabolic and inflammatory, 245
Hypertension, 277
 arterial, and tetraethylammonium, 807
 desoxycorticosterone in, 33
 in dextrocardia, 304
 nor-epinephrine and epinephrine, 807
 paroxysmal, with tabes dorsalis, 729
 seminars on (E.), 783
Hysteria, case of, 272

Immunity in syphilis, 641
Infarction
 myocardial, and rupture of heart, 775
 in dextrocardia, 304
Insulin mixtures, 532

Jaundice, 912

Letterer-Siwe's disease, 245
Lipids, liver, in cirrhosis, 188
Liver
 carcinoma of, 561, 570
 cirrhosis of, 188
Lung, carcinoma of, and deep x-ray, 148
Lupus erythematosus disseminatus sine lupo, 288
Lysozyme
 in peptic ulcer, 482
 ulcerative colitis, 496

Massachusetts General Hosp. clinic on psychosomatic problems
 A case of hysteria, 272
 Feeble-mindedness or pseudoretardation, 891
Meigs' syndrome, 237
Meningitis
 Friedländer bacillus, in diabetes, 470
 pneumococcal, 402, 449

Metabolism, nitrogen, effect of injury and disease on, 100
Mononucleosis, infectious, 912

Nebulization and intermittent positive pressure breathing in pulmonary disease, 853
Nephritis, glomerular, 548
Nephrotic syndrome, 548
 and lupus erythematosus, 288
Neuropathy, visceral, and diabetes mellitus, 610
Neurosyphilis
 penicillin in, 712
 spinal fluid findings in, 709
Nitrogen metabolism, effect of injury and disease on, 100
Nor-epinephrine, epinephrine and hypertension, 792
Nutrition, parenteral, 749

Obesity, 277
Oxygen therapy in rheumatic carditis, 379, 392

Pain, chest, and fatal termination, 599
Paragonimiasis, pulmonary, 167
Pelvic tumors with ascites and hydrothorax, 237
Penicillin
 in acute endocarditis, 908
 bacteremia and pericarditis, 298
 neurosyphilis, 712
 subacute bacterial endocarditis, 202
 treatment of syphilis, 679, 687, 702
Pericarditis, and bacteremia treated with penicillin, 298
Peripheral vascular collapse and congestive heart failure, 126
Peripheral vascular disease, 433
Pneumococcal meningitis, 402, 449
Pneumothorax and mediastinal emphysema, 59
Poison oak, dermatitis of, 548
Potassium intoxication, electrocardiographic manifestations of, 821
Porphyria, acute, 53
Pressure breathing, intermittent positive, and nebulization in pulmonary disease, 853
Problems of convalescence (E.), 165
Propylthiouracil, and agranulocytosis, 48
Protein
 food, parenteral, 760
 hydrolysates, 879
 and pure amino acids, 879
 selection of, 586
 utilization of, 419
 therapy, evaluation of, 264
Pseudomonas aeruginosa in bladder, 76
Pseudoretardation or feeble-mindedness, 891
Psychosomatic medicine, 857
Pulmonary atelectasis in stuporous states, 210
Pulmonary disease, intermittent positive pressure breathing and nebulization in, 853
Pulmonary paragonimiasis, 167
Pyoderma gangrenosum in ulcerative colitis, 69

Renal excretion of penicillin and subacute bacterial endocarditis, 202
 Respiratory disease, hemolytic streptococcus, and anti-streptolysin "O," 3
 Retrospect and prospect, 1948 (E.), 1
 Rheumatic carditis, oxygen therapy in, 379, 392
 Rheumatic fever, electrocardiographic changes in, 365
 Rice and low sodium diets, effect of, on arterial blood pressure, 815

Seminars on protein hydrolysates

Amino acid mixtures as parenteral protein food, 760
 Assessment of knowledge concerning the clinical use of protein hydrolysates and pure amino acid mixtures, 879
 Chemical considerations in the selection of protein hydrolysates, 586
 Effect of injury and disease on nitrogen metabolism, 100
 Problems in the evaluation of protein therapy, 264
 Problems of parenteral nutrition, 749
 Utilization of protein hydrolysates by normal and protein-depleted animals, 419
 Serology in syphilis, 670
 Serum potassium
 abnormalities of, and electrocardiographic disturbances, 828
 influence of, on electrocardiogram in diabetic acidosis, 838
 Simmonds' disease, 462
 Sodium amytal and pulmonary atelectasis, 210
 Spinal fluid findings in neurosyphilis, 709
 Splenic infarct, rupture of, and bacterial endocarditis, 143
 Staphylococcus aureus and acute endocarditis, 908
 Streptomycin
 effects of, on *Pseudomonas aeruginosa*, 76
 in Friedländer bacillus meningitis, 470

Syphilis
 epidemiology of, 655
 immunity in, 641
 prenatal, prevention and treatment of, 693
 serologic tests for, 670
 symposium on (E.), 629
 treatment of, with penicillin, 679, 687, 702
 Syphilitic infection, biology of, 631

Tabes dorsalis and hypertension, 729
 Tetractylammonium in arterial hypertension, 807
 Thephorin in allergy, 44
 Thiouracil hepatitis, 138
 Thrombocytopenic purpura, 912
 Thrombophlebitis migrans with involvement of sinuses, 916
 Thrombosis, venous, and pulmonary embolism, 716
 Thyroid disease, antithyroid agents in, 90
 Tuberculosis, venous thrombosis and pulmonary embolism in, 716

Ulcer

peptic, bleeding, 503
 "intractability" in (E.), 479
 lysozyme in, 482
 Uremia, extrarenal, 574

Washington Univ. clinico-pathologic conferences
 Acute, severe chest pain with fatal termination, 599
 Diabetes, fever of unknown origin and coma, 898
 Obesity, hypertension, diabetes and heart failure, 277
 Pneumococcal meningitis, 449
 Progressive congestive heart failure with peripheral vascular collapse, 126

